*THE BIRTH OF EFFICIENCY* • *HELLO, HELLO, DOLLY, DOLLY* • *ANTISENSE DRUGS*

# THE SCIENCES

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## THROUGH THE LOOKING GLASS

*The Strange, Disorienting World of Noncommutativity*

*by* DANA MACKENZIE

THE SCIENCES

MAY/JUNE 1997
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# Initial Conditions

EDITOR S NOTEBOOK

## Mirror, Mirror

WHO HAS NOT SUCCUMBED TO A FASCINATION WITH THE SYMMETRIC world that lies, in Lewis Carroll's memorable phrase, "through the looking glass"? Part of the fascination, no doubt, comes from the subtlety of the imperfections in the reflection. The person one sees shaving or straightening a wave of hair seems preternaturally familiar, yet underneath the breast in the image a heart seems to beat on the right. Our cover photograph, *True-False,* by the Russian-born artist duo Rimma Gerlovina and Valeriy Gerlovin, expresses part of the ambivalence many people feel in confronting their mirror counterpart. What fatal flaw lurks beneath the surface image? How close is perfection to its opposite: how delicate the differences between happiness and sadness, love and hate, good and evil, truth and falsehood, the sacred and the profane?

Our cover story on noncommutativity by Dana Mackenzie (page 32) explores the far-reaching mathematical consequences of allowing mirror-image expressions much like "5 + 7 = 7 + 5" to be false. In "Dollars and Antisense" (page 24) Sudhir Agrawal tells the story of the rise of a multimillion-dollar industry founded on the principle that DNA and RNA must form symmetric, complementary counterparts to serve as templates for making proteins. And in "Disorderly Conduct" (page 15) Hans Christian von Baeyer shows how subtly the natural forces of entropy can operate: an asymmetry in the laws of physics that confers a direction to time.

Perhaps imperfections and asymmetries can help explain the immediate, visceral aversion that many people have to human cloning. As Diana Lutz reports in her Quanta story, "Hello, Hello, Dolly, Dolly" (page 10), the scientific realities of Ian Wilmut's singular achievement with the now-famous lamb Dolly have been all but forgotten by the mainstream press. In their place has been a frenzy of revulsion combined with self-absorption, perhaps partly expressing a deep public antipathy toward single parenthood, as people try to imagine cloned human beings who look just like thee and me. But in a cool hour one has to wonder: Just how quickly, and how often, will even Wilmut's result be replicated? How readily does the technology generalize to mammals other than sheep? As the developmental biologist Scott F. Gilbert of Swarthmore College remarked to me, there is more time for "reprogramming" transplanted DNA in the early sheep embryo than there is in the embryos of, say, a mouse or a human being—perhaps making sheep much the easier to clone.

More, will Dolly develop into a sexually mature adult or turn out to be as sterile as a mule? Will she be prone to early cancer, heart disease or other infirmities of aging inherited from the DNA of a six-year-old sheep? Or has the mammary-cell DNA from which she grew somehow been shorn not only of its particular, adult cellular identity, but also of age itself, by a bath in a cytoplasmic fountain of youth? The answers to those and other questions are at least as important to the ultimate ethical acceptability of human cloning as are the current aversions to it.

"Clone" comes from the Greek word for twig. Suppose the mechanisms of mammalian reproduction turn out to be as straightforward to manipulate as the branches of a fruit tree: what then? A cloned person would be a time-shifted identical twin of its donor, no more, no less. The environmental differences of the two people, so central to their ultimate character that the differences can affect brain chemistry, could be at least as great as the ones affecting identical twins reared apart: as the twig is bent, so grows the tree. Those differences would include the reasons a cloned child's parent(s) chose to procreate by cloning—reasons that would undoubtedly affect the child's psychological development. A second feature of the child's environment would surely be discrimination: how much "clonism" would a human clone have to endure from the "sexually reproduced" majority?

*The Sciences* will have much more to say about cloning in future issues of the magazine. In the meantime, we would hope that cool heads will prevail and that research into animal cloning will not be held hostage to premature fears that baby clones are just around the corner.

—PETER G. BROWN


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# Peer Review

LETTERS FROM READERS

*Fanny Brennan,* Mont St. Michel, *1977*

## "KIND" RACISM

In his essay, "Bred in the Bone?" [March/April], Alan H. Goodman's citation of the extra left leg that showed up after the Oklahoma City bombing is unjustified. In fact, a number of mistakes were made in handling that case and I made my share of them. But the error he accuses me of making was not the one I made.

It is not considered ethical for forensic scientists to comment publicly on their findings in ongoing homicide investigations. To fully explain the complexities and interactive errors involved in the case would require reference to or release of documents and reports currently sealed by the courts. Only when the trials of the defendants Timothy J. McVeigh and Terry Nichols are complete will it be possible to present a full analysis of the "left leg" case. After the trials are over, my colleagues and I plan to publish such an analysis in a refereed scientific journal.

In his closing paragraph, Mr. Goodman, citing Donal Muir's dichotomy of "mean" and "kind" racists, implies that I am either one or the other. As far as I am concerned, the term "mean racist" is redundant and the idea of such a thing as a "kind racist" is oxymoronic.

In the past decade my work devoted to the investigation of the disappearance, torture and extrajudicial execution of human rights victims in many countries has often made me the target of public criticism and official outrage. To date, however, none of my critics has called me a racist. Among my detractors have been apologists for the brutal military junta in Argentina, representatives of General Pinochet's military in Chile, the Guatemalan Defense Minister and Serbian government spokesmen. Thus Mr. Goodman finds himself in interesting company.

CLYDE COLLINS SNOW

*Norman, Oklahoma*

**Alan Goodman replies:** It was not my goal to detail any errors of practice that were made in the identification of the left leg. Rather, my point is that the key mistake, an all-too-common one, was to adopt a racial world view. When one classifies people as being closer to the white or the black "racial type," which is, after all, what is done by the statistical formulas used in this case, it is inevitable that the wrong "race" box will sometimes be checked. In medicine, such an error is an example of ideological iatrogenesis. The world view causes harm.

I am aware of Mr. Snow's forensic work on the identification of victims of state violence, and I greatly admire it. My essay, however, was about an entirely different subject. Its main point was to show that the everyday use of race in science—what others call racialism or scientific racism—is somewhat analogous to Muir's idea of "kind" racism. The continued use of an outdated concept serves to perpetuate the sense that races are real, and it may eventually aid real racists.

## WAVES AND PARTICLES

In Hans Christian von Baeyer's Physika essay, "The Quantum Eraser" [January/February], the proposed resolution of the wave–particle duality he reports on is a bit hasty.

Mr. von Baeyer discusses two sets of circumstances: (1) a beam of untagged quantons passes through a double slit and arrives at a scintillating screen; (2) a beam of quantons that are tagged according to the slit they passed through arrive at a scintillating screen. The tagging is done by inducing an "up" or "down" spin component in some chosen direction, depending on which slit they went through, and it makes no difference whether the tagging is done in front of the slits or behind them.

The point that Mr. von Baeyer apparently missed is this: In both sets of circumstances the patterns on the screen are wave patterns. In the first circumstance it is a double-slit interference pattern; in the second circumstance it is a combination of two separate diffraction patterns corresponding to the two slits. Hence the usual statement about the wave–particle duality, namely, that quantons travel as probability waves and, when hitting a screen, manifest themselves as particles, holds for quantum erasers as well as for other experimental setups.

SHIMON MALIN

*Colgate University*
*Hamilton, New York*

*Continued on Page 47*

**Working Hypotheses**

# Sweet Reason

BY RODNEY W. NICHOLS

*President and CEO, the New York Academy of Sciences*

MANY YEARS AGO I LEARNED A LESSON ABOUT "SWEET REASON." I HAD ENTERED a curbside debate with a group opposed to all experiments with animals. I pointed out that vaccinations of children (and animals!) against infectious diseases would be neither safe nor effective without exploratory work with animals. A young activist said he didn't care about that. I noted that new surgical techniques could not be proved reliable—nor could new surgeons be trained—without testing on animals. An elderly woman responded that any sacrifices of nonhuman life conflicted with her religion. On and on went the exchange, respectful and nonviolent, but stymied. My sweet reasons cooled the fire of a few activists, and the activists conveyed a great deal to me about their convictions. But the exchange led to no general agreement. When values conflict, I learned, the reasons cited in their defense are unlikely to persuade the other side—especially when the relevant science, in this case, toxicology, is underdeveloped.

Of course, such impasses are hardly confined to questions about animal experimentation. And they raise a deep and troubling issue: Can conclusions based on values be reconciled with conflicting conclusions based on reason? In some circles, for instance, sociologists, literary critics and philosophers question whether modern science has any special status as knowledge. Informed skepticism need not be a "flight from science and reason," as one of our recent *Annals* put the matter. Often it is not. But when it is, ad hominem charges may be played out in the press. Positions freeze as tempers boil, and the scientific enterprise risks losing the confidence of the public.

Popularized exaggerations of such scholarly quarrels resemble the distortions that were aired in courtrooms a few years ago, when highly speculative arguments were invoked about the risks of the antinausea compound Bendectin and the dangers of the breast-implantation procedure. In their forthcoming book, *Judging Science: Scientific Knowledge and the Federal Courts,* Kenneth R. Foster and Peter W. Huber illuminate the uncertainties of such risk assessment and map how science, even with its provisional nature, can be credited as valid. The U.S. Supreme Court, in its 1993 decision in the case of Daubert *v.* Merrell Dow Pharmaceuticals, strengthened the guidelines for weighing the admissibility of evidence purporting to be scientific into the courtroom. Citizens and jurors must develop an appreciation of what constitutes scientific validity if they are to be enlightened by analysis, not confused by hyperbole.

Yet what is one to make of ominous attacks arguing that modern science and technology may steamroll human freedom, homogenize cultural differences, even crush spirituality? Einstein gave one ringing answer: "Science without religion is lame, religion without science is blind." What I think he meant to underscore is that values count, whether in the traditional framework of religious belief or in secular systems based on honesty, fairness and a compassionate civil society. Rapidly modernizing democracies can embrace rapidly unfolding technologies without sacrificing humane goals and social traditions. With dedication to tolerance and pluralism, all freedoms and economic progress flourish.

Still, choices must be made, and those decisions will always blend science with values. Most of our instrumental knowledge with wide applications is universally valid and beneficial—the knowledge needed for building computer chips, for instance, for constructing bridges, for reducing pollution. A clash of values rarely arises here, although choices that turn on economic trade-offs will always reflect values. But instrumental knowledge is not the only basis for action, the only expression of the powerful drives to explore the natural universe and apply the lessons that life and inquiry teach. As Pascal said: "The heart has its reasons that reason knows nothing of."

These issues cry out for thoughtful and open debate, with rational analysis serving as a crucial arbiter in achieving consensus. The recent dramatic news about cloning draws attention to the imperative for expanded dialogue. I invite you to let us know what you think about the roles of values, reason and science in the modern world. ●

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*John Wilde,* Still Further Festivities . . . , *1991*

CITATIONS

# Bi-fi

*Cloning stories that no longer seem so futuristic*

WHILE SCIENTISTS, ETHICISTS and policy makers have had only a few months to ponder the potential implications of human cloning, sci-fi writers and moviemakers have been doing it for years. Fiction, unlimited by scientific or ethical constraints, offers a clone for all occasions. In some future worlds, as in C. J. Cherryh's book *Cyteen* (1995), laboratories artificially grow workers and soldiers that are computer-trained to serve the purposes of society. Clones crafted by hand require more care. Both in *Cyteen* and in Ira Levin's book *The Boys from Brazil* (1976), a clone is exposed to the same environmental influences as the original, in an attempt to produce the same person.

Cloning is more serious and less common in Arthur C. Clarke's novel *Imperial Earth* (1975). The clones of the childless founder of a human colony on Titan are bred to ensure genetic heirs, but not to be exact duplicates of the father.

What else is cloning good for? To cook up an army for an alien with delusions of world domination, of course. The low-budget 1965 movie *The Human Duplicators* is a must for any alien who needs a recipe. Dreams (or nightmares) of an all-female society are realized through cloning in Poul Anderson's book *Virgin Planet* (1959) and in Charles Eric Maine's novel *World Without Men* (1958).

Clones of presidents, dead and alive, populate the pages of Ben Bova's *The Multiple Man* (1976) and Nancy Freedman's *Joshua, Son of None* (1973). And try to imagine what clones were used for in the 1978 movie, *Parts: The Clonus Horror.* From the grotesque to the psychological: a man obsessively studies his clone in a quest for self-knowledge in Gene Wolf's book *The Fifth Head of Cerberus* (1972), and a child learns the truth about herself and her unnatural origins in the 1983 movie *Anna to the Infinite Power.* And—surprise, surprise—the cloned dinosaurs (and dollars) from *Jurassic Park* are back in a sequel, *The Lost World,* which premieres May 23 in the United States.

In the world of cloned armies, duplicate geniuses, multiple Hitlers and resurrected dinosaurs, cloning a mere sheep seems practically boring. —MEHER ANTIA

CELLULOID

**Going the Way of Pompeii—**Brimstone rains down on the entertainment capital of the world as the La Brea tar pits erupt in *Volcano,* Hollywood's latest natural-disaster movie. Tommy Lee Jones runs an overwhelmed Los Angeles emergency service, setting a grittier tone than Pierce Brosnan, who played the daring but charmingly instructive volcanologist in this winter's *Dante's Peak.*

FROM THE PODIUM

**Space Is the Place—**James R. Zimbelman of the National Air and Space Museum discusses the future of Mars exploration in "A Return to the Red Planet," May 7. John Mather of NASA's Goddard Space Flight Center talks about successors to the Hubble Space Telescope in "The Next-Generation Space Telescope," June 4. Both lectures are free. 7:30 P.M. Einstein Planetarium, at the National Air and Space Museum in Washington, DC. Phone: 202-357-2700.

GATHERINGS

**Third International Conference on Functional Mapping of the Human Brain—**Copenhagen, Denmark. May 19–23. Phone: 45-42-92-44-92. Web: http://orkide.lab3d.odont.ku.dk/~pet/HBM97/index.html

**Eighth International Global Warming Conference and Exposition—**Columbia University, New York, NY. May 26–29. Phone: 630-910-1551. E-mail: syshen@megsinet.net

**Year 2000 International Symposium—**Topic: Strategies for correcting system date processing arising from millennium change. National Institute of Standards and Technology, Gaithersburg, MD. June 9–10. E-mail: judith.newman@nist.gov. Web: http://www.nist.bov/y2k

GADGETRY

## America the Digital

*A relief for the eyes*

Its bland title, "Landforms of the Conterminous United States—A Digital Shaded Relief Portrayal," gives not a scintilla of a hint of the eye-popping vividness of this fascinating black-and-white map. Computer-generated from satellite imagery, the 35-by-57-inch map is billed as "the largest single-sheet graphic of relief forms of the U.S. since the classic hand-drawn oblique map . . . by Raisz (1939)." Without the usual clutter of place names, political divisions and, frankly, color, the map aims instead for stark contrast in resolving landforms as small as a mile across. The payoff is unprece-

*Agnes Denes,* Isometric Systems in Isotropic Space, Map

dented textural richness in the sweep of physical relief from the folded Appalachians to the Rocky Mountains and the Pacific. Particularly intriguing is the stunning detail in the vast area of low-relief between those ranges, and the barrier islands along the Atlantic and Gulf coasts appear as exquisite fractal filigree. An accompanying booklet explains how the map was generated. Best of all, it's cheap: Map I-2206 costs $4, plus $3.50 handling. Order from the U.S. Geological Survey, 800-USA-MAPS (800-872-6277).

—M.B.A.

**109th Annual Meeting of the Astronomical Society of the Pacific**—Hyatt Regency Chicago. June 27–July 2. Phone: 415-337-1100. Web: http://www.aspsky.org

## ON DISPLAY

**Rivalries Revisited**—The space race, which epitomized the tense competition between the U.S. and the former Soviet Union, is rapidly receding into the pages of history. *Space Race* catalogues the rocket rivalry between the two countries as they raced to launch spy satellites, nuclear warheads and men into space. Highlights include a space suit designed for the never-realized Soviet moon landing and a camera from the world's first spy satellite. Opens May 16 in the Space Hall of the National Air and Space Museum in Washington, DC. Phone: 202-357-2700.

**Better Than Clue**—At the *ChemMystery* exhibit *you* are the forensic scientist who visits the scene of the crime. Then you get to analyze handwriting, fingerprints, DNA and powder residues—with genuine chemical tests—to find out whodunit. Mysteries are geared separately to youngsters and to older children and adults. Through Sept. 1 at the Lawrence Hall of Science, Berkeley, CA. Phone: 510-642-5132. Web: http://www.lhs.berkeley.edu

**Splendid Silent Sun**—Solar power as a catalyst for design is the theme of *Under the Sun,* an outdoor exhibit that ranges from sundials to light-sensitive surfaces to working solar collectors. Through mid-October at the Cooper-Hewitt National Design Museum, New York, NY. (Passersby can view the exhibit on Fifth Avenue and 90th Street both day and night.) Phone: 212-860-6868.

***Poles Apart***—Thirty photographs, paired by Arctic and Antarctic, show polar inhabitants and terrains. Through Aug. 4 at the National Museum of Natural History, Washington, DC. Phone: 202-357-1300.

## AT THE ACADEMY

**Conferences:**

(For registration information, phone: 212-838-0230, ext. 324.)

**IXth International Conference on Myasthenia Gravis and Related Disorders**—Loews Santa Monica Beach Hotel, California. May 7–10.

**Seventh Cooley's Anemia Symposium**—Royal Sonesta Hotel, Cambridge, MA. May 30–June 2.

**Ultrasound Screening for Fetal Anomalies: Is It Worth It?**—Rockefeller University, New York, NY. June 23–25.

**Sections:**

(Unless otherwise noted, all events take place at the New York Academy of Sciences, 2 East 63rd Street, New York, NY, and start at 7:30 P.M.)

**Long Term Fate of PCBs in the Hudson River**—Edward A. Garvey, TAMS Consultants, Inc. Sections of Environmental and Geological Sciences. May 5.

**Neuroimmunomodulation: A Minisymposium**—Sections of Neuroscience and Biomedical Sciences. 3:00–6:00 P.M. May 6.

**Parallel Computing: Issues and Insights**—Albert Y. Zomaya, University of Missouri and University of Western Australia. Section of Computer and Information Sciences. May 13.

**Will the Mountain Gorilla Survive the 21st Century?**—Dieter Steklis, Rutgers University. Section of Anthropology. May 13.

**Physics of the Modern Tennis Racket**—Howard Brody, University of Pennsylvania. Section of Physics and Astronomy. May 15.

## JUST FOR KIDS

### Eye of Newt and Toe of Frog

After enticing 7-to-12-year-olds with backyard insect expeditions, the second installment in the Junior Nature Guide series sets the kids off in search of amphibians and reptiles. The integrated activity package includes a CD-ROM and book on

*Scherer & Ouporov, Birth Cycle, 1993*

how to attract, collect and identify common amphibians and reptiles. A companion Web site <http://www.natureguides.com> includes some worthwhile science links for kids. Compatible with Macintosh and Windows 3.1 and 95. $29.95, from ICE, Inc., Toronto, Canada. Phone: 416-868-3294.

## PHENOMENA

**Meteor Shower**—Eta Aquarids peak, May 5.

**Solstice**—Summer (in the northern hemisphere) and winter (in the southern hemisphere) begin, June 21, 4:21 A.M. eastern time.

## SUMMER STOCK

**Speaking in Tongues**—"Languages in Linguistics" is the theme of the 59th biennial summer institute sponsored by the Linguistic Society of America. Cornell University, Ithaca, NY, June 23–Aug. 1. Phone: 607-255-4987. Web: http://www.sce.cornell.edu/CUSS/LSA.html

**A World of Your Own**—Practice monitoring and managing the environment of a mini-planet while earning four credits from Columbia University at the Biosphere 2 campus in Oracle, AZ. Summer session of the Earth Systems Field School runs July 28–Aug. 22. $4,500. Application deadline, June 30. Phone: 800-992-4603. Web: http://www.bio2.edu/education/camp.htm

**Down by the Sea**—Sea World/Busch Gardens Adventure Camps offer week-long introductions to marine biology for middle- and high-schoolers at sites in Florida and Texas. Phone: 800-4Adventure (800-423-8368).

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## THE TUBE

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—COMPILED BY MARY BETH ABERLIN AND MEHER ANTIA

# Hello, Hello, Dolly, Dolly

*What's really new with cloning? Developed cells can return to their embryonic state.*

*Olivia Parker,* Missing Piece–Ibis, *1993*

"Frankenstein's monster" cried the popular press in response to the announcement from Scotland that an adult ewe had been cloned. The reference was probably inevitable: the mammary-gland cell that supplied the DNA for making a lamb was an "adult body part," fused with an egg cell by a jolt of electric current. But the media clearly didn't have in mind the pitiful, self-loathing student of Goethe in Mary Wollstonecraft Shelley's classic novel. What they meant instead was Boris Karloff with bolts through his neck. Does it matter?

At a background press conference on cloning and its ethical implications, convened at the New York Academy of Sciences in New York City a few days after the epochal announcement was made, an eight-member panel—a developmental biologist, three medical doctors, a biotechnology company executive, a lawyer, a bioethicist and a rabbi—agreed that the cloning story had turned into a caricature of itself. In the process much of the scientific news had been missed.

Alan R. Fleischman, senior vice president for medical and academic affairs at the New York Academy of Medicine, called the visceral reaction of the public to the announcement more interesting than the scientific achievement itself. Erik Parens, a bioethicist at the Hastings Center in Briarcliff Manor, New York, agreed. Both cheerleaders and doomsayers alike share the same mistaken idea, he said: that you can clone a self. "But as everyone in this room knows, you can't clone a self," Parens noted, "because a self is a function of infinitely more than one's genetic material."

Several panelists argued that the issue of cloning the human species is a red herring, simply because it isn't practical, desirable or even likely. Parens, building on his point about the cloning of a self, wondered what effect that idea, however mistaken it might be, would have on culture and politics.

Roy M. Goodman, a New York state senator who was in the audience at the press conference, gave Parens what amounted to an instant answer to the political question. What did the panelists think, he asked, of legislation proposed by New York State Senator John J. Marchi that would make it a felony to proceed with human cloning in the state? Fleischman said he saw no reason for rapid-fire legislation, because the ability to clone a human won't come any time soon. Marie A. DiBerardino, a developmental biologist at the Medical College of Pennsylvania–Hahnemann School of Medicine in Philadelphia, agreed, though she said she would welcome a ban on human cloning.

Having disposed of Frankenstein's monster, the panelists sought to give a better account of just what the embryologist Ian Wilmut and his coworkers at the Roslin Institute in Edinburgh, Scotland, had done in their now-famous experiment. According to DiBerardino, who characterized herself as "the oldest cloner, or nearly the oldest one," the procedure of nuclear transplantation used by Wilmut was developed by Robert Briggs and Thomas J. King in Philadelphia as long ago as 1952. First tested in amphibians, the procedure was soon extended to insects and fishes and, in the 1980s, to mammals.

All those experiments, however, began with embryonic cells—cells that have not yet differentiated, or become specialized for a particular physiological function. Although Wilmut admitted he did not determine whether the donor DNA came from mammary tissue or from a relatively undifferentiated mammary stem cell, the donor cell was still far more specialized than any cell from an embryo. When Wilmut's new lamb, Dolly, emerged from the transferred DNA of an adult sheep, what Wilmut had achieved was, most of all, the cloning of a differentiated cell.

That was partly what made the popular accounts of the sheep cloning so puzzling—and so misguided. Many of them distinguished between cloning an embryo and cloning an adult. But had the point really sunk in, the story of cloning a monkey from an embryo cell, which broke soon after Wilmut's announcement, would have been ignored.

The panelists also sought to correct another widespread misconception: that an adult clone is a carbon copy of its parent. The clone and parent need not be identical for at least three reasons. First, not all of a cell's DNA lies in its nucleus. A cell's mitochondria, the organelles that fuel cellular reactions, also contain DNA, and the mitochondrial DNA invariably comes from the egg. Unless the nuclear DNA from the parent were transplanted into an egg from the parent's mother, a clone would not genetically match the parent at every level. Second, the DNA in an adult cell differs from the DNA in a fetal cell by a lifetime's worth of damage.

But the main point, stressed by several panelists besides Parens, is that even "iden-

tical" twins are not identical. Any animal is the product not just of its genetics but also of its environment, both in utero and after birth.

Not everyone agreed that such distinctions are important. Rabbi Marc Gellman of Temple Beth Torah in Melville, New York, rebuked his fellow panel members for logic chopping. "There is a wisdom in common people, in ordinary people," he said, "who have been unfairly demeaned by people who view their lack of knowledge about haploid and diploid and totipotent embryos as somehow a disqualification to have moral sensibilities. . . .There is a strong and real understanding that we are not our own creators. And this technology undermines that fundamental belief in the most powerful and disturbing way possible."

THE PANELISTS, HOWEVER, SEEMED LESS arrogant than dismayed—deeply dismayed that much of the public discussion assumes that people are the products of their DNA alone. The irony of the New York Academy session was that men and women who have devoted their lives to the study of DNA were urging the audience not to overestimate its role in their lives.

So if cloning human beings is impractical, unethical and unlikely, what use is Wilmut's experiment? Dean L. Engelhardt, senior vice president of Enzo Biochem, Inc., in New York City, said cloning would improve the process of animal husbandry by enabling animals with genetically desirable traits to be bred more efficiently. Indeed, the more sober newspaper accounts suggested that Wilmut's work probably would lead to the cloning of the nation's best milk cows rather than of humans.

But Jon W. Gordon, a professor in the departments of obstetrics/gynecology and geriatrics at Mount Sinai School of Medicine in New York City, raised practical objections to such ideas. Gordon has done in-vitro fertilization with humans as well as mice, and he has done gene-transfer experiments in mice. Cloning will never replace selective breeding as a method of genetic engineering in animals, he said. For one thing, cloning halts any further progress: once you've cloned a cow, for instance, you can't keep breeding that version for greater milk production. Gordon also opposes schemes for using cloning to mass-produce "therapeutic" tissues or proteins.

If cloning is not a panacea for agricultural or medical problems, why does it interest scientists? DiBerardino may have given the best answer when she said: "It's possible to take a kidney carcinoma cell nucleus from a frog and inject it into an enucleated egg and get a swimming tadpole. Not more tumor masses, but a swimming tadpole. So the molecular milieu of the [egg] cytoplasm has dictated that the normal genes turn on and the genes causing the proliferation turn off." In other words, every cell holds within its nucleus the information needed to make every kind of cell in the body and, indeed, to make a whole frog, or rabbit, or person. But during development those nuclear recipes are somehow selectively turned off or blocked. As a result, the cell is no longer totipotent, or capable of giving rise to an entire, fertile organism. The lesson of Wilmut's experiment is that the modification of the nuclear DNA is reversible.

—DIANA LUTZ

# Qubit by Qubit

*Building a better quantum computer*

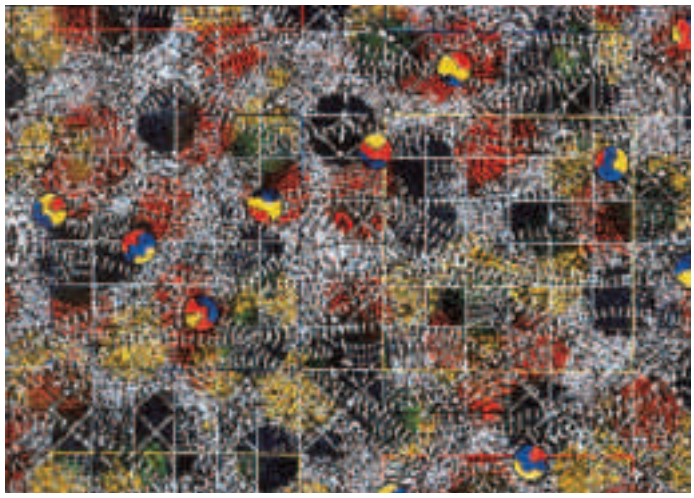
FOR ALL THEIR APPARENT SPEED, MODern computers can still be excruciatingly slow. Indeed, banks and military communications depend on the security afforded by that sluggishness, by making would-be code breakers factor hundred-plus digit numbers into their fifty-plus digit primes in order to read or forge a private message. Even with today's supercomputers, you would need on the order of $10^{20}$ years (roughly 10 billion times the age of the universe) to factor the 1,000-digit product of two 500-digit primes. Three years ago Peter W. Shor took that thought experiment a step further. A mathematician at AT&T Labs in Murray Hill, New Jersey, Shor devised a superfast method of factoring that could take advantage of the remarkable laws of quantum mechanics, which govern the behavior of matter and energy at atomic dimensions. A quantum computer running Shor's algorithm could factor any 1,000-digit number in about half an hour.

Shor's work hinted at the mind-numbing potential of quantum computing—and plenty of future work for cryptographers. But it was purely hypothetical. Investigators have dreamed about quantum computers for more than a decade, but most considered them nearly impossible to build. In order to take advantage of the laws of quantum mechanics, the computational processors would have to be well-insulated from the rest of the world. In the past, investigators have gone to heroic lengths to achieve that state even for a single atom. Now, however, two physicists have found a way to solve the problem with relative ease. Neil A. Gershenfeld of the Massachusetts Institute of Technology and Isaac L. Chuang of Los Alamos National Laboratory in New Mexico published their work in the January 17, 1997, issue of *Science*. Even an ordinary cup of coffee, they conclude, could be turned into a quantum calculator.

IN AN ORDINARY COMPUTER, INFORMAtion is represented and processed by simple physical systems that can have one of two states, generally labeled 0 or 1: a switch that can be either on or off, a capacitor that can have either high or low charge. A system in one of two such possible states stores one bit of information. One or more bits can be processed or combined through so-called logic gates. For example, a NOT-gate flips a bit, that is, it changes an input 1 to a 0 or an input 0 to a 1. An AND-gate combines two bits in such a way that the output is a 1 only if both inputs are 1s (otherwise the output is a 0).

Suppose, in the interests of miniaturization, you decide you would like the spin of a single atomic nucleus to represent the 0s and 1s of computation. The spin of a nucleus is quantized: unlike the axis of a spinning top, whose direction can be measured simultaneously along all three spatial axes, nuclear spins, though randomly distributed in any bulk sample, can be measured along only one spatial axis at a time. Hence they can be described as pointing in only one of two directions, conventionally called *up* or *down*. The *up* and *down* states can serve perfectly well to represent ordinary computation with 1s and 0s.

But nuclear spins, according to the rules of quantum mechanics, can also be in the *up* and *down* spin states simultaneously. What that means is that if you were to measure the spin, you would find, with some probability $p$, that the spin points *up* and, with the complementary probability $1-p$, that the spin points *down*. A bit that exists in a superposition of two such states is called a qubit, or quantum bit. As long as you



*Andrea Way,* Quantum Jump (detail), *1990*

*Continued on Page 45*

JOHN FLEISCHMAN

# The Archaeologists Who Wouldn't Dig

*Uncovering one of the most storied sites in antiquity—without touching a shovel*

In all of Greek literature, there are few places more famous than Pylos. "Sandy Pylos" is Homer's epithet in the *Iliad* for the kingdom of Nestor, the garrulous old warrior-king who gives the other Greek captains so much unwanted advice before the walls of Troy. In the *Odyssey,* Telemachus begins his search for his lost father, Odysseus, at Nestor's palace. Perched at the southwestern tip of modern-day Greece, Pylos was also the site of a scandalous event during the Peloponnesian War: the surrender, in 425 B.C., of some 120 armed Spartan officers of the hoplite infantry to the Athenians. "Nothing that happened in the war," the historian Thucydides noted, "surprised the Hellenes as much as this."

In our century nothing has matched what happened at Pylos on April 4, 1939, probably the luckiest first day on a dig an archaeologist ever had. On that morning Carl W. Blegen, the preeminent American archaeologist of the time, opened a trench through an olive grove. There, above Pylos, he struck what he later described as "the office of internal revenue" in Nestor's late Bronze Age palace. A cataclysmic fire had destroyed the palace 3,200 years earlier, but storage jars of olive oil had exploded near clay tablets on which the palace financial records were kept, firing them into a crude ceramic. All told, Blegen laid bare more than 1,000 tablets covered in an early Greek script called Linear B, the earliest writing then known on the European mainland.

A terrible disappointment to some classicists (who had hoped the tablets would be filled with poetry), the decipherment of Linear B was a revelation to historians. The *wanax,* as the king of Pylos was called, had made his scribes keep lists of everything: bath attendants, bronze-shod chariot wheels, perfumed oil and postings of shepherds and coastguards. The Bronze Age Greeks, or Mycenaeans, such lists show, had created the first highly centralized civilization in Europe—a precursor to city-states, empires and nations from Athens to the Soviet Union.

For Jack L. Davis, Carl W. Blegen professor of Greek archaeology at the University of Cincinnati in Ohio, that was reason enough to revisit Pylos fifty years after his predecessor's first excavations. Davis assembled a consortium of archaeologists, historians, physical scientists and students into the Pylos Regional Archaeological Project, or PRAP, including John Bennet of the University of Wisconsin-Madison, Susan E. Alcock of the University of Michigan in Ann Arbor, Cynthia W. Sheldmerdine of the University of Texas at Austin, Yannos G. Lolos of the University of Ioannina in Greece and Eberhard Zangger, founder of Geoarchaeology International in Zurich, Switzerland.

*Mark Tansey,* Robbe-Grillet Cleansing Every Object in Sight, *1981*

In archaeological parlance, PRAP is "survey." By plotting the locations of ceramics, stone tools and other artifacts that weathered out of the soil across wide areas, PRAP determines large-scale patterns of human activity. The shovel is the one tool that Davis and his fellow principal investigators do not use. PRAP does not dig.

Archaeologists who don't excavate? Surely that is heresy. Yet surveys are a well-established archaeological practice. American anthropologists working in the Southwest and in Meso-America refined the technique in the 1960s and 1970s. Later, British archaeologists picked up the New World habit, wedded it to French modernist theories on the history of "ordinary" life and brought it to bear on Old World problems. Still, nothing as ambitious as the PRAP survey has ever been tried on mainland Greece. "It's one thing when you find a hundred or even a thousand artifacts in a square kilometer," Davis says of North American surveys, "but in the Aegean we're finding hundreds of thousands of artifacts in a square kilometer."

The results of that work are already available on the World-Wide Web at <http://classics.lsa.umich.edu/PRAP/html>. The really subversive stuff, however, is in Davis's mild-mannered book titled *Sandy Pylos,* which will be published by University of Texas Press next year. *Sandy Pylos* quietly undermines many conventional assumptions about archaeology and history. Without lifting a shovel, Davis's teams have uncovered nothing less than "the history, not just of one archaeological site, but of an entire landscape," as Davis writes in the book's foreword, "and not just in a single period, but at all times in the past."

THE LOCATION OF PYLOS WAS AN ancient mystery even to the ancients. As the Greek geographer Strabo noted, quoting an old riddle: "There is a Pylos in front of Pylos and there is yet another Pylos." Even Greeks of the Classical Age knew only that Nestor's Pylos lay near the town they called Koryfasion (not to be confused with modern Koryfasio, which is somewhere else entirely).

When I decided to retrace Blegen's footsteps and talk with Davis, I had to take an all-day bus ride from smog-bound Athens across the rocky Peloponnesus to Pylos in western Messenia. Eight hours later, dehydrated and reeking of tobacco smoke, I staggered off the bus in Pylos and fell straight into the confusion over place names in modern Greece. In 1827, after the Greeks won their independence, the Ottoman town of Navarino was renamed Pylos. But Ottoman Navarino had never been ancient Pylos. The Pylos I was looking for turned out to be a short but terrifying taxi ride away: fourteen kilometers north of town, along the Bay of Navarino and then several hundred yards abruptly uphill, to the beak of a sharp ridge called Ano Englianos.

Blegen's dig is now covered by a huge, open-sided sheet-metal hangar, erected by the Greek government to protect the low, rubble footprint of the late Bronze Age palace. The day after my arrival, I wandered through the ankle-high maze of the palace remains in search of the great central *megaron,* or throne room, where the wanax presided. From scraps of fallen plaster, Blegen had reconstructed some of the palace's brilliant decorations. There were frescoes of deer, doves, bare-chested warriors, a singer and his lyre: a splendid setting for a warrior-king—even one surrounded by accountants. Down the hall, the Linear B archives never bothered to name the king, but they did name the place.

This was Pylos, the Pylos before there were any others. Standing outside the ruin, looking across the plain below to the Bay of Navarino and the Ionian Sea beyond, I could understand why the later Greeks could not find Pylos: they were convinced that Homer's "sandy Pylos" had to be near the sea. Why Pylos was here in the hills was a question PRAP would later answer for me.

A journalist visiting a working archaeological site usually can count on a grand tour of the "dig," a tortured plot of ground covered with grid markers, tools and heaps of dirt waiting to be screened. There, in the holy trenches, he will be shown graduate students with serious sunburn working the earth with dental picks and dustpans.

Davis did not have a single trench to show me. Survey work is done by walking, he explained as we sat in the cool of the evening at PRAP headquarters in the village of Hora. Every morning between fifteen and twenty PRAP students fan out in teams across the rugged hills and coastline around the old palace. At fifteen-meter intervals they pace off precise quadrants, collecting surface artifacts and environmental data. (Areas covered with dense litter are resurveyed more intensively.) The teams press on regardless of topography, heat and the infamous Greek *macchia,* chaparral-like underbrush that grows luxuriantly even where shepherds and their goats have given up.

Fresco, Pylos, *Late Bronze Age*

At day's end the PRAP walkers carry their surface finds back to a temporary museum in a Hora schoolhouse. There the finds' locations are logged in a marvelous computer information base and the sherds are stored in recycled five-gallon oilcans.

BROKEN POTTERY IS A VIRTUALLY CATastrophe-proof record of human settlement. Invaders may loot precious metals and survivors may scavenge building materials, but no one ever carries off the broken pottery—no one, that is, except archaeologists. Aegean pottery types, from the truly ancient to the nearly modern, have been so thoroughly characterized that PRAP pottery experts can usually sort the fragments as easily as if they were sorting socks.

At many archaeological sites, soil stratigraphy is everything: it gives context to artifacts, showing when and how they were deposited and what the environmental conditions were at the time. But farmers have churned up Western Messenia for 6,000 years; in some places the ground has eroded so deeply that they plow up the soft bedrock marl directly for soil. Over time the surface of the soil has become a historical hodgepodge: bits of late Bronze Age oil jars are mixed indiscriminately with eighteenth-century Ottoman plates and third-century Roman roof tiles. Nevertheless, as sherds weather to the surface, they create a rough statistical model of what's below. Collected and plotted, the age-sorted sherds pile up electronically around certain sites, indicating peaks of activity and population. Survey is about finding such patterns.

READERS WHO DIP INTO *SANDY PYLOS* for the "truth" behind Homeric epics or Greek nationalism will be swept away instead by a torrent of time rushing across Messenia. The book synthesizes new data, old documents and novel analyses, and it draws perspectives from at least a dozen disciplines. The evidence comes from everything from core drilling to medieval financial records newly uncovered from state archives in Istanbul and Italy.

The story begins with the clash of the African and Eurasian tectonic plates that pushed up the Taygetus Mountains as well as other chains running from Greece to the Balkans. Two million years of stream erosion went on to create two rugged coastal valleys, and a series of ice ages left the slopes covered with pine forests. Then, in about 15,000 B.C., people first began to leave traces of their habitation.

Evidence of farming dates from about 4000 B.C., first in the form of light tools along stream bottoms and then, after 3000 B.C., in the form of plows. In the next 1,000 years both the human population and the number of grazing livestock exploded. Those explosions set off the first of what pollen and soil samples show were four waves of dramatic environmental change, which gradually wiped out the native vegetation and stripped away most of the topsoil. The second wave coincided with the rise of Mycenaean culture in about 1400 B.C. and the third, in about 500 B.C., with the new intensive agricultural practices of the Classical world. PRAP's physical scientists charted those changes, concluding, for instance, that in the fourth century B.C. olive trees were cultivated on a quarter of the surface area of the Pylos region. The fourth, last and ongoing wave of destruction dates from modern times, with the rise of the bulldozer and the chemical sprayer.

Each wave of environmental change marks a major change in human activity, or—in the common parlance—history. Take those olive groves. Here the environmental and archaeological survey data come together in intriguing ways. Until PRAP, the early Classical period was the black hole of the Messenian past. In the eighth century B.C. Sparta swallowed up its western neighbor in a series of shadowy wars, and the Spartan grip was not broken until 371 B.C., when the Spartans were defeated by the Theban general Epaminondas at the Battle of Leuctra. The Spartans had little interest in recording their own history, much less the history of the subjugated people of Messenia. Only through the curiosity of other Greeks, particularly such nosy Athenians as Thucydides, can contemporary scholars glimpse the fate of Spartan vassals, who were reduced to the status of *perioikoi* (literally

"dwellers around"), with no political rights, or to helots, who were state-owned slaves. What were the Spartans up to for all those centuries before Messenia regained its independence?

Elsewhere in Greece at that time numerous scattered farmsteads were the agricultural rule. But in Messenia PRAP found no sherds from Spartan-era farmsteads. After reviewing PRAP's exhaustive survey records, the archaeologists Ann B. Harrison, of the J. Paul Getty Museum in Los Angeles, and Nigel Spencer, of the Institute of Archaeology of the University of Oxford in England, concluded that such farmsteads never existed on the PRAP site. Instead the population was crowded into large villages and small towns—so that their Spartan overlords could control or overawe them, presumably—and the olive groves were tended by helots. With the defeat of Sparta, PRAP's sherd patterns also show, the population spread out through the countryside.

IF THE PRAP SURVEY MARKS THE changes in the landscape, it also reveals the continuities. Long before the Spartans came to Pylos, an indigenous Mycenaean palace culture arose from a scattering of small fiefdoms, then slowly formed a centralized kingdom. That evolution can be seen in sherd patterns and in the location of Bronze Age *tholos* tombs. By the late Bronze Age anyone who was anyone in Mycenaean Pylos was buried near the palace on Ano Englianos. Other secondary settlements faded out completely in the late palace period, their populations drawn away perhaps by the brighter lights of splendid Pylos.

Scouring the countryside for every sign of previous settlement, PRAP was able to locate 150 separate sites, many of which may number among the 240 places named in the Pylos Linear B tablets. By matching the restored geography to the activities recorded on the tablets, and by referring to the work of previous scholars, John Bennet (one of PRAP's resident Linear B specialists) could draw an amazingly detailed picture of the kingdom of Pylos, which covered close to 800 square miles. The kingdom had a "Hither" province of seven districts, it seems, and a "Further" province of nine, divided by Mount Aigaleon, rising to the northeast of the palace.

Seeing that line on the map, I suddenly knew why Strabo and the Greeks of the Classical Age couldn't find Pylos. The palace was sited in the shadow of the mountain, not to keep an eye on the distant sea but to keep an eye on Hither and Further. The wanax of Pylos ruled both sides of the mountain. His palace guarded the pass between them.

But the wanax had nautical interests too. The closest thing to an amazing "find" for PRAP was the discovery of the Bronze Age harbor of Pylos. It was a manmade, 360-by-250-yard straight-sided basin created by diverting part of the Selas River across an alluvial plain. The basin is "the first and thus far only artificial port discovered in prehistoric Europe," according to Eberhard Zangger, the geoarchaeologist who headed PRAP's earth sciences team.

Although no port structures (let alone ships) have yet been found, the PRAP geologists inferred the construction of a port from core samples that bore marine remains dated to the twelfth century B.C. In the layering of fine clays and then coarse gravels, Zangger could read the sudden transformation of a calm, shallow pond into a deep basin fed by the redirected Selas surging toward its new outlet. Excavations elsewhere in Greece had revealed the Mycenaean knack for diverting streams to control floods and supply water. Here they had turned that talent to building a harbor in the shadow of the wanax's palace.

*LAYERS OF FINE clays and gravels have revealed evidence of the only artificial port yet discovered in prehistoric Europe.*

The port perished soon after the palace. Without a central authority at Pylos, the walls of agricultural terracing that surrounded the palace could not be maintained. As the walls collapsed, they spilled hillsides of rich soil into the sea, and the harbor silted shut.

THE *GÖTTERDÄMMERUNG* OF THE PALace haunted earlier archaeologists. Blegen read into the destruction of "Nestor's Pylos" the advent of the "Dorian" invasion, which was the traditional explanation in Classical times, as well as in Blegen's, for the overthrow of the Mycenaeans. All their great strongholds perished in the late twelfth century B.C., plunging Greece into a dark age (the Geometric period) that lasted for 500 years in Pylos. Blegen flatly declared that the great fire at Pylos ended human occupation on Ano Englianos.

"That's not what happened," Davis told me. "That's not true at any site. People just don't walk away unless a volcano goes off suddenly and they have absolutely no warning. Very often they gradually abandon their sites rather than all at once. They return to sites. They carry off stuff of value. And they build on top of the sites, often 1,000 years later."

That's what PRAP shows happened at Pylos. Life went on in the old kingdom without the wanax. PRAP walkers collected many sherds of Geometric pottery in a wide swath around the palace. Those sherds were then linked to Geometric material that Blegen recovered inside the palace ruins—sherds he had dismissed as trivial later intrusions. The pottery may have become cruder, such examples show, the agriculture rougher and the population smaller, but the locals remained, speaking Greek and worshiping the same gods.

Davis doesn't believe in a Dorian invasion or occupation. "As far as I'm concerned, there's no evidence for any displacement or entrance of foreigners at this time," he said. "The evidence points to continuity. Mycenaean pottery is related to the pottery of historical Greece. It's hard to believe it wasn't the same population."

IT'S HARD TO BELIEVE THAT ANY LANDscape could have as much history as Pylos. Except for a brief Messenian "independence" after the Spartan expulsion, the region has been a pawn of greater powers. Ruled from Rome and then Constantinople, Messenia was ravaged by the Heruli, the Visigoths and the Vandals, two major earthquakes and various plagues. The Middle Ages brought the Venetians for the first time, followed by a conquering Frankish knight, Geoffroi de Villehardouin of Champagne, driven by a storm to the coast south of Pylos during the Fourth Crusade in 1205. Frankish "Morea" was swept, in turn, by Catalan mercenaries, imperial troops reasserting Byzantine authority, the Black Death, the Venetians again, the Ottoman Turks (for the first time), the Venetians yet again and the Ottoman Turks (for the second time) before its liberation in 1827.

PRAP draws the historical line at Greek independence, but you might as well throw in the Second World War, the Greek civil war and membership in the European Community, which, by allowing foreigners to buy land along the coast, is unleashing rampant development on ancient sites.

The damage worries Davis, but it does not surprise him. People have lived around Pylos since the Neolithic. At least since the second millennium B.C., he figures, some of the inhabitants have come from the same, Greek-speaking stock. That is not to say the Pylians are "pure" Greek in a narrow ethnic or nationalistic sense. The population has always been well mixed, thanks to warlords, mercenaries, refugees, slaves, holy men, merchants, tourists and archaeologists. Dealing with such a mix of ancient and modern, of legends and ledgers, is the whole point of survey archaeology. In Greece "the problem confronting surveyors is not in finding artifacts," Davis writes, "but in investigating, in a systematic manner, an entire landscape full of them." ●

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HANS CHRISTIAN VON BAEYER

# Disorderly Conduct

*Order always seeps away toward chaos, but the ways of entropy can be passing subtle*

*Alfredo Castañeda,* The Lady of the Mirror, *1986*

"JUST LOOK AT THIS mess," I grumble at my thirteen-year-old daughter Madelynn, as I tug at a loose sheet of notebook paper covered with scribbles that is sticking out of a bookshelf in her room. "Put that back," she snaps indignantly. "That's my homework, and it was exactly where it belonged. You don't understand anything!" She slams the door. We do not see eye to eye. Where I find chaos, she perceives perfect order.

Order is an elusive concept. In science its meaning is no less ambiguous than it is in Madelynn's room. Consider a hologram recorded on a photographic plate: it looks like a jumble of splotches and whorls, devoid of pattern, shape or order. Yet laser light shining through it creates a nifty 3-D image of the Taj Mahal, revealing the order hidden under apparent disorder. Conversely, observe the blank portion of a CD. Its surface seems as smooth and shiny as high technology can make it—the embodiment of featureless order. But under a microscope that level plane becomes an unruly heap of atoms piled higgledy-piggledy like pebbles on a beach. Like beauty, order—and disorder—can lodge in the beholder's growing understanding.

In view of such apparent subjectivity it is surprising that order, unlike beauty, is a precise and powerful instrument in the tool chest of science. The man who put it there was the Austrian theoretical physicist Ludwig Boltzmann, who more than a century ago made the astonishing claim that entropy is molecular disorder, and that the second law of thermodynamics—the law of increasing entropy—can be interpreted simply as the tendency for things to become more disorderly.

On the face of it, entropy is a straightforward, measurable property of matter, like the length of a ruler or the weight of a rock. Applied to a melting ice cube, for instance, it is given by the ratio of the heat absorbed in the melting process, to the temperature of the ice on the Kelvin scale (273.15 degrees Kelvin)—two quantities that can readily be measured in the laboratory. That such a simple, albeit mystifying, ratio should in any way relate to the chaotic quivering of invisible molecules, and specifically to a property as arcane as their degree of orderliness, seemed so unlikely to Victorian physicists that many dismissed Boltzmann's work as quixotic. Yet history proved him right, and today's schoolchildren learn the bland maxim that entropy is disorder.

THE CONCEPTUAL BRIDGE THAT ENabled Boltzmann to connect the quantitative term *entropy* with the intuitive concept of disorder was the idea of probability. In any collection of molecules an orderly arrangement is improbable, and so it is assigned a low entropy. A messy, disorderly arrangement, on the other hand, is common and probable; accordingly, it corresponds to a higher level of entropy.

Madelynn's room illustrates the connection. Order is defined as the state in which all her books rest on their shelves in the same upright position. Madelynn prefers them scattered over the floor in arbitrary orientations; because many more ways exist to achieve such an arrangement than there are ways to put the books on the shelves, the helter-skelter state is more probable than the "orderly" one. In other words, if you were to toss the books into her room at random, they would be far more likely to land on the floor than on the shelves. No matter how she may define it, physicists call the more probable state more disorderly. In that way the subjective terms "order" and "disorder" are quantified by association with probability and identified, respectively, with low and high entropy.

The second law of thermodynamics, applied to Madelynn's room, simply states that in the natural course of events the room has a tendency to become more disordered. To be sure, order can be restored, and entropy lowered, but only at the expense of energy on the part of Madelynn—or of her parents. An ice cube melts according to the same principle. The fixed, orderly arrangement of water molecules in the precise rows and columns of an ice crystal gives way naturally to their formless, fluid disarray in water. Freezing them back into ice again is possible, but only at the expense of the electrical energy consumed by a refrigerator. (In the winter so much hidden order lurks in the sluggish motion of atmospheric molecules that the process reverses: liquid water discards its disorder into the air and turns spontaneously to ice.)

Such illustrations help make Boltzmann's interpretation of entropy seem compelling to the point of self-evidence. In fact, though, it remains rich in strange, counterintuitive implications. A startling exam-

ple of the subtlety of the concept of order has emerged from a series of experiments done recently by a team of physicists including Anthony D. Dinsmore, Arjun G. Yodh and Peter D. Kaplan, all at the University of Pennsylvania, Jennifer L. Rouke at the University of Rochester in New York, and David J. Pine of the University of California, Santa Barbara. The investigators work in a wonderland of their own making. Instead of studying atoms or molecules in all their quantum-mechanical complexity, or following computer simulations that skirt the danger of oversimplification, they focus their attention on simple yet real systems of huge numbers of particles. Their universe is a drop of water under a videomicroscope, and its population a vast collection of microscopic polystyrene balls.

A SOUP OF IDENTICAL PLASTIC PELLETS floating in water is a reasonable, if somewhat uninteresting, model of a gas. When a batch of such particles is introduced into the droplet, the particles disperse and, in accord with the law of entropy, spread out like a gas into every available nook. Furthermore, like the atoms or molecules that make up a gas, the pellets continually bounce off each other as well as the glass walls of their container. The density of the polystyrene is such that the balls float practically weightlessly in the drop of water, and so gravity plays no role in any of the experiments. The diameter of each little sphere is approximately a hundred nanometers, or a tenth of a micron—roughly a hundred times smaller than the width of a human hair. All one can see with the naked eye is a drop of milky water whose appearance stays the same for weeks at a time.

But things change dramatically when the investigators switch to a mixture of particles of two different sizes—a high concentration of small pellets interspersed with a relatively small number of balls whose diameters are roughly ten times larger. A gymnasium full of flying tennis balls jostling a sprinkling of medicine balls conveys the image. When the workers first prepared this gruel, it resembled the homogeneous liquid, but after a period of between twelve and forty-eight hours a change became apparent to the naked eye. The glass walls of the little pond began to cloud over and then developed a kind of crust.

When the investigators examined the crust under a microscope, they were surprised and delighted to see what looked like a bag of jewels strewn onto the glass. Brightly colored rubies, sapphires, amethysts and diamonds seemed to sparkle in the light of the microscope—only their shapes were wrong. They were formed not in the familiar crystalline geometries of gems, but in flat lozenges and hexagons.

The different hues were not hard to understand—they were caused by an effect discovered long ago in the context of X-ray scattering from atoms. But how could the gemlike structures form in the first place? Ordinary crystals grow from atoms that attract each other and stick together electrically. Plastic balls, by contrast, exert no forces on a wall or on each other until they touch—and then they repel and rebound. Finding fixed, orderly structures in that drop of water was as unexpected as it would have been to discover rigid pyramids made of medicine balls, hanging like stalactites from the ceiling of a gymnasium. Worse, crystals are highly ordered arrangements of particles; what business did they have growing spontaneously out of a chaotic mixture? How could the precipitation of such colorful gems be reconciled with the entropy principle? Was the second law of thermodynamics, which has been called the supreme law of nature, so feeble it could be subverted by a simple suspension of plastic balls in a drop of water?

SAILORS ONCE BELIEVED *that two large ships sailing close together would be mysteriously drawn toward each other. The sailors were right.*

FURTHER INVESTIGATIONS WITH AN electron microscope proved that the colorful platelets of the crust were indeed made up of regular arrangements of the larger balls, built up to about five balls thick. But what was the "glue" holding the platelets together? Two observations proved to be essential clues: The platelets grew only along the walls, and they were made up only of the large balls. From those clues the investigators could identify the culprit: it was the small pellets that held the platelets together. And the gluing mechanism, remarkably simple in itself, created the conditions in which the new and subtle illustration of the entropy principle emerged.

The attractive forces on the platelets arise from what is called a depletion force, which the pellets transmit against the large balls. Imagine for simplicity that a large cube, instead of a large ball, is approaching a flat wall, all the while keeping one face parallel to the wall. As long as the cube is still a substantial distance away, pellets pummel it with equal force on all sides and from all directions; the result is that the pellets exert no net force on the cube.

If, however, the cube gets close enough to the wall that the pellets can no longer squeeze into the gap between the cube and the wall, something new happens. The impact forces of the pellets on the four faces of the cube perpendicular to the wall still cancel each other out. But the collisions of the pellets with the face approaching the wall suddenly cease, leaving the collisions on the face farthest from the wall to act on the cube alone. A net force develops on the cube, pushing it toward the wall.

More generally, in any suspension of particles of two different sizes, the larger ones, regardless of shape, are attracted toward the walls of the container and toward each other by the depletion force. The encrustation of the larger particles on the walls of the container in the Dinsmore experiment was a clear signal of a depletion force at work.

Variations of that force, which is caused by the shielding effect of the larger objects, have a venerable history. In the eighteenth century the respected botanist Cadwallader Colden became obsessed with finding the cause of the force of gravity. The conceptual model he came up with explains gravity as the differential pressure of invisible particles of ether, which are supposed to fill the universe. Because the earth and the moon partly shield each other from the impact of particles that come from far away, the pressure is smaller on the sides of the earth and the moon that face each other. The two large bodies are therefore allegedly pushed together—though the force they undergo has none of the well-known characteristics of gravity. Colden's model was immediately rejected by those who understood physics.

Another variant of the depletion force substitutes water waves for plastic pellets and ethereal corpuscles. Nineteenth-century sailors believed that two large vessels lying parallel and close together on a windless sea with a big swell experience a kind of attractive force. Such a force could be disastrous, because it could draw the ships together and entangle their rigging. Last year the Dutch physicist Sipko L. Boersma of Delft wondered whether the mysterious force is real or just another maritime yarn. His conclusion, supported by a simple theoretical calculation, was that it does indeed exist. It is caused by the depletion of certain kinds of waves that pound the ships from the outside but cancel each other in the space between the hulls.

THE DEPLETION FORCE EXERTED BY pellets accounts qualitatively for the attraction between large polystyrene balls, and it explains how they manage to cluster together. But it leaves unanswered the enigma of their increased order. The solution, suggested nearly forty years ago by two Japanese physicists, is both ingenious and simple—a fine illustration of nature's subtlety in enforcing its laws, as well as an object lesson on the meaning of order. It turns out that even as the large balls attract each other and increase their orderliness, the small pellets become more disordered. The growing entropy of the pellets more than compensates for the increasing order among the large balls, and saves the second law of thermodynamics.

To understand how such a surprising assertion can be correct, imagine a closed container full of floating pellets of uniform size. The disorder among the pellets arises partly from their random distribution and partly from their erratic motions, but it also comes about simply by virtue of the volume they occupy. If the pellets were corralled into a smaller space in the container, their orderliness would be higher, their entropy would be lower and they would tend to disperse. (Madelynn's room is similar: if all her things were shoved pell-mell into a closet, the room would temporarily assume a high degree of orderliness—a fact that she has unfortunately discovered on her own, even though she has never heard of Boltzmann.) If, on the contrary, the pellets encountered a hole in their container, they would seize the opportunity to increase their entropy—and fill a larger volume. The point is that the entropy of the pellets increases with the volume they can occupy.

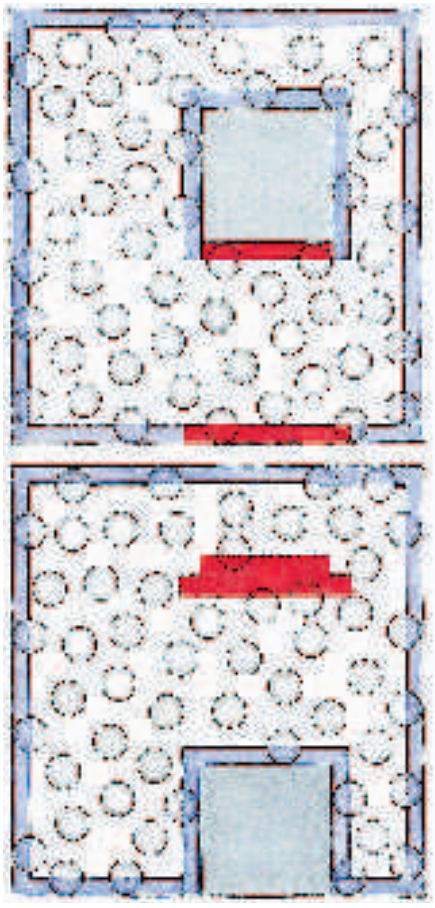
Strictly speaking, though, the space available to the pellets is not the entire volume of their container. Since they are not point particles but rather have a small, nonzero radius, their centers cannot touch the walls. The volume over which the centers of the pellets can roam is therefore that of the container, minus the volume of a forbidden region that covers the inside walls to a thickness of one pellet radius. In view of the minuscule size of the pellets, such a diminution of lebensraum seems insignificant, but it turns out to be crucial.

Now introduce into the vessel once again a large cubical particle. Centers of pellets are excluded not only from the volume of that cube, but also from a layer one radius thick enveloping it [*colored regions in the upper illustration at right*]. When the cube touches a wall, the volume available to the centers of the pellets increases by the volume of the excluded layer over one face plus the volume of the excluded layer along the wall the cube now occupies. [*The space released to the centers of the pellets corresponds to the red region in the lower illustration at right.*] Thus the motion of the cube toward a wall actually increases the entropy of the pellets. The argument calls for an analogy.

IMAGINE A FENCED PLAYGROUND WHERE children can roam at will. Unfortunately, the power company needs to place a small transformer in the middle of it and, for safety, to surround the transformer with a circular fence enclosing a hundred square feet. The parents are unhappy that the area of the playground will shrink. When the power company announces it will add a second transformer, the parents voice loud complaints at the prospect of losing 200 square feet of playing space.

Then one clever parent points out that if the two transformers were put right next to each other, the common fence around them wouldn't rob the children of much more than a hundred square feet. The discovery suggests that if the two transformers were now moved to the side of the playground, or better yet into a corner, the wasted space could be cut back to a mere twenty-five square feet—an eighth of what had been feared. (Compare the area of a quarter circle surrounding two nearly coincident points in a corner, with the area of two nonoverlapping circles somewhere in the middle of the playground.)

It turns out that maximizing the area available to the children creates a tendency for transformers to cluster together and to move toward the outside. In the same way,



maximizing the volume and entropy available to pellets, as the second law decrees, creates a pressure on large objects toward the walls and toward each other. In fact, the spaces between them are minimized when they are arranged in a crystal pattern. For this reason the attraction felt by plastic balls can also be called an entropic force.

There remained one last step in Dinsmore's investigation. The push of the pellets on a single plastic ball had to be isolated and compared with the strength of the push that would be predicted from the simple geometric theory of excluded volume. Although it is not too hard to manipulate a single polystyrene ball, it turned out to be exceedingly difficult to watch it move under the influence of the entropic force. The reason for the difficulty is that the force is zero at some distance and then suddenly becomes strong at short range. As a ball approaches a wall, it undergoes no attraction at all, until suddenly, at a separation of only one pellet diameter, it snaps onto the wall and clings like a magnet. Mapping out the variation of the force over that minuscule distance proved virtually impossible.

But last fall Dinsmore and his colleagues finally succeeded in tricking their little world to give up its last remaining secret. Realizing that it is easier to study motion along a surface than motion perpendicular to it, they placed a large ball ("large" in this context means one-half micron in diameter) near the edge of a microscopic glass terrace. What held the ball there was not gravity, which was neutralized by buoyancy, but entropic attraction. That same force also kept the particle from drifting off the terrace. Typically the ball would slither around, approach the edge of the abyss, hover there for a while and then retreat to the safety of the terrace, driven by the incessant pounding of the small pellets. Patiently the investigators repeated the procedure hundreds of times, filming each attempt with the video-microscope and comparing it with a prediction made on the basis of simple geometry. The close agreement between theory and observation constituted the first direct measurement of an entropic force, and a confirmation of the theory.

NOW THAT THE PRINCIPLE IS UNDERstood, it may find applications in technology. By etching patterns onto a surface—a grid of terraces like so many mesas, for example—molecules and particles in emulsions could perhaps be controlled by entropic forces. Whether techniques that exploit entropy instead of fighting it will result in the development of better paints, electronic devices or lasers remains to be seen.

But the more philosophical lesson of the work is already apparent. It demonstrates with unusual clarity how order can arise spontaneously at the expense of hidden disorder. Creationists who maintain that the emergence of the exquisite order of living organisms out of the chaos of the inanimate universe violates the law of entropy would do well to learn from this example. Not surprisingly, the intimate relation between order and disorder can also be appreciated from a less mechanical, more intuitive point of view. The American poet Wallace Stevens, for instance, titled one of his poems "Connoisseur of Chaos." There he put the matter bluntly:

> A. A violent order is disorder; and
> B. A great disorder is an order. These
> Two things are one.

Madelynn would agree. ●

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# TAYLOR-MADE

*How the world's first efficiency expert refashioned modern life in his own image*

BY ROBERT KANIGEL

*Frank Gilbreth,* Motions Necessary to Move and File Sixteen Boxes Full of Glass, *1917*

THROUGH CAJOLERY, threats, fines and firings, Frederick Taylor, a young foreman in a Philadelphia steelworks, had by late 1880 succeeded in doubling the work done by the skilled machinists working under him. For the moment, the men were cowed and his bosses were happy with him. But he himself was miserable. "I was a young man in years," he said later, "but I give you my word I was a great deal older than I am now with worry, meanness, and contemptibleness of the whole damn thing. It is a horrid life for any man to live, not to be able to look any workman in the face all day long without seeing hostility there." He would get out of the business altogether or else, as he said, "find some remedy for this unbearable condition."

The "remedy," as he came to see it, was knowledge.

Taylor worked in the machine shop of the Midvale Steel Company, where forged steel locomotive axles and rimlike "tyres," some weighing half a ton or more, were cut to size with such tools as lathes and boring mills. Those great belt-driven machines could cut metal only so fast without burning themselves up or prematurely dulling their tool bits. But how fast was that? How should the machines be set?

Taylor would have liked to tell his men: "You're running it way too slow. With this kind of steel, and that depth of cut, and that feed, you should be able to go at twenty feet per minute, easy. Use these pulleys here." But he couldn't say that, because he didn't know for sure. The grizzled machinists under him would say, "No, that's too fast. It'll burn up the tool. It'll wreck the machine." But they didn't know either, not really; much of their wisdom was guesswork, built up over the years into serviceable rules of thumb. Besides, what was the big hurry? For them informed guesses were good enough.

For Taylor they were not. To find out just how fast the tools could cut, he undertook a series of experiments. Ultimately, the variables in almost any metal-cutting operation—speed, feed, tool shape, the kind of metal being cut and so forth—could be reduced to a mathematical problem solvable, on a special slide rule, in twenty or thirty seconds.

Taylor's experiments went on for twenty-six years. But even the earliest Midvale tests yielded tables and charts able to supply machine settings that depended relatively little on a machinist's judgment. Soon, as Taylor wrote later, first-class machinists were being replaced "by men who are trained up from a lower class of work," typically laborers or machinists' helpers. Traditional craft know-how, reduced to scientific data, was passing from workman to manager, from shop floor to front office. On the big boring mills at Midvale, Taylor was creating a new world of work.

FREDERICK WINSLOW TAYLOR, STILL JUST twenty-five when he began his experiments and only a few years out of his apprenticeship, was the world's first efficiency expert. His ceaseless quest for "the one best way"—the phrase that came to be associated with him and the whole efficiency movement—influenced Henry Ford and Lenin and moved the management guru Peter F. Drucker to include him, along with Freud and Darwin, as one of three seminal makers of the modern world.

To the organized labor of his day Taylor was a slave driver. To the bosses he was an eccentric who *raised* wages while ruling the factory floor with a stopwatch. To himself he was a misunderstood visionary who, under the banner of science, would confer prosperity on all and abolish the old class hatreds. To millions today who feel they give up too much to their jobs he is the source of that fierce, unholy obsession with "efficiency" that marks modern life. "Why is it so easy," Michael W. Munley, then at the University of Massachusetts in Amherst, asked in a 1991 doctoral dissertation, "to hear and see reminders of Frederick Taylor in the brusque efficiency with which affluent American professionals organize their lives . . . [with] personal planning calendars, car telephones, voice mail, [and] beepers to track them anywhere, even on vacation?"

By one definition Taylorism is "the application of scientific methods to the problem of obtaining maximum efficiency in industrial work or the like." Or the like. And in that slight, almost parenthetical extension lies a hint of Taylorism's hold. Because though Taylor got his start in the factories of the industrial Northeast in the 1880s, it is not just the workplace that bears his imprint today but modern life in general.

Scholars have laid at Taylor's door phenomena as various as the evolution of "leisure," from genuinely free time to organized recreation; the Reagan Administration's approach to managing the federal bureaucracy, and even what the late historian and social critic Christopher Lasch has called a "new interpretation of the American dream." Various writers have seen Taylor's hand in the work of the poet William Carlos Williams; in the French modernist writer Louis-Ferdinand Céline's call for an industrialized, standardized medical-care system; in the rigid daily timetables meted out to Alcatraz inmates during the 1930s.

Since 1910, when Taylorism was propelled from the narrow precincts of industry into the consciousness of the world, it has become a ubiquitous presence, for good and ill, in modern life. And it was Midvale Steel in the early 1880s to which its roots reach back.

SOON AFTER HE came to Midvale, Taylor recorded in his notebook that a bricklayer and helper laid, on the average, 480 bricks in a ten-hour day. That kind of straightforward observation was nothing new; similar notes had been made a hundred years before by the Scottish economist Adam Smith in *The Wealth of Nations,* and by generations of shop foremen and owners. But soon after Taylor embarked on his metal-cutting experiments, he began to ask a different question. Not, How long does a job take to complete? But, How long should it take? Taylor's early notebook entries were History. The new questions, viewed the right way, were Science.

Sources from Taylor's time, some of which he may have consulted, suggested that a man could accomplish between one-and-a-half million and four million foot-pounds of work in ten hours. But Taylor decided to do his own experiments: he offered workers double pay, warned them their windfall would be over at the first sign of slacking off, gave them arduous tasks and calculated the work they did per day in foot-pounds and its rate in horsepower. But the tests still yielded nothing consistent enough to use in computing a man's wages.

In these experiments Taylor and his assistant used a stopwatch to time the work they gave the men; with it they could as easily measure what a man did in ten seconds as in ten hours. Sometime in 1883, Taylor wrote later, it "occurred to [me] that it was simpler to time each of the elements" of a job and establish an overall time for it by adding up those times than it would be to search through records of past jobs and guess how they might apply to a future one.

Taylor had found a hidden bonanza: in breaking work into its components, you were almost forced to study it. What got in a workman's way? How could a machine be modified? Which operations could be improved, which eliminated? At first, work might seem no more than a featureless smear of movement. But after a while it was as if you were seeing it in slow motion, each element of it highlighted, dissected, splayed open for view.

An early subject of time study was the manufacture of locomotive tires Taylor had investigated in his first metal-cutting experiments. Formerly, the workmen earned a fixed amount for turning each tire to size. But once Taylor was through, their job was no longer to machine a tire but was a succession of smaller tasks: Set tire on machine ready to turn. Rough-face front edge. Finish-face front edge. Rough-bore front. And

*Man Ray,* Indestructible Object, *1923/1958*

so on, each step minutely described and timed to the tenth of a minute.

Taylor had seen his experiments as balm for the ill will on the shop floor: by recourse to an impartial arbiter—ever fair-minded science—he and his men would be able to rise above mere opinion, with its raised voices, to serene and stable fact. Once the time-study man had finished and a clerk had added up his columns of numbers, the time needed to machine an axle or overhaul a boiler warranted no further discussion: the numbers spoke for themselves.

Or did they?

IN TAYLOR'S MIND, AT LEAST, WORKING MORE efficiently did not necessarily mean working harder. And yet, to yield to the stopwatch, to keep relentlessly on task, took something out of you that the older, looser ways did not. The work itself might be no more physically demanding. But somehow, by day's end, it felt as if it were. You had to do things now in the one best way prescribed for you, not in your old, idiosyncratic and less-efficient way. And no self-respecting workman liked that.

"It is one thing to know how much work can be done in a day," Taylor realized, "and an entirely different matter to get even the best men to work at their fastest speed or anywhere near it." To get them to conform, he learned, you had to pay them more.

How much more?

The answer, Taylor would write with a shrug of sarcasm years later, was not a "subject to be theorized over, settled by boards of directors sitting in solemn conclave, nor voted upon by trade unions." Rather, it was dictated by "human nature," and he had established it through more experiments. Back at Midvale he had approached half a dozen workers with a deal: On a particular job they would get a 15 percent premium. But they had to do it in precisely the way Taylor decreed. "When we tell you we want you to use such and such feed and such and such speed," as Taylor put it, "we want you to use it." After some months, they could go back to the old way, at the old wages. Or they could continue in the new way, at the new wages.

The decisions of the workmen constituted the data of Taylor's experiment. Along with the men making 15 percent more, he set up other groups, paid an additional 20, 25, 30 or 35 percent. How much would it take to buy them off? The experiment gave the answer, establishing the pay that just barely overcame the workmen's resentment at having to keep to the stern beat of Taylor's drum and not their own.

And there it was—the Faustian bargain in embryonic form: You do it my way, by my standards, at the speed I mandate, and in so doing you will achieve a level of output I ordain, and I'll pay you handsomely for it, beyond anything you might have imagined. All you have to do is take orders, give up your way of doing the job for mine.

*Mike Mandel,* Emptying the Fridge, *1985*

*Mike Mandel,* Wrapping Sandwiches, *1986*

If you went along with the bargain, the promise went, efficiency improved, production shot up, wages shot up. Decades of refinement lay ahead—generations of industrial engineers who would work out the details, conduct experiments, write books and treatises. In later years Taylor would get a laborer, immortalized as "Schmidt," to go from loading fourteen tons of pig iron a day to loading fifty-two and a half. But by about 1884, at Midvale Steel, most of the essential elements of the Taylor system were already in place. Ahead lay a harmonious new industrial future.

That, anyway, was the idea.

TAYLOR'S DISCIPLES WENT ON TO INSTALL HIS system in factories around the country. Taylor lectured to rapt audiences of industrialists and was named president of the American Society of Mechanical Engineers. Yet he was still known only within his profession. That changed in 1910, when a group of

Eastern railroads petitioned the Interstate Commerce Commission for a freight rate increase. In the hearings that ensued, the future Supreme Court Justice Louis D. Brandeis dismissed the petitioners' request; they could save far more than the millions they sought, he said, by embracing the efficiency methods of a Philadelphia genius named Frederick Winslow Taylor. Soon Taylor and "scientific management," as it became known, were on every industrialist's lips and efficiency was a national ideal.

Organized labor, however, saw Taylor as out to destroy the workingman's health and rob him of his manhood. The novelist Upton Sinclair observed how Taylor's showcase laborer, Schmidt, got just 61 percent more pay for 362 percent more work. A correspondent for *American Machinist* magazine pictured the Taylorist worker as "simply one of the gears in the operation of the machine." Samuel Gompers of the American Federation of Labor and other labor leaders denounced Taylor in bitter broadsides.

*Mike Mandel,* Changing Diapers, *1985*

Finally, after workers at a government arsenal in Watertown, Massachusetts, went out on strike against time study, a Congressional committee held months-long hearings to "investigate the Taylor and other systems of shop management." The hearings were capped by four grueling days of testimony by Taylor, in which congressmen and labor leaders relentlessly interrogated him. When Taylor spoke of how the "first-class man" profited under his system, chairman William B. Wilson pointedly asked about the fate of those not first-class. When Taylor contended that a proper day's work was a matter of "accurate, careful scientific investigation," Wilson wondered how disinterestedly scientific it could be when the employer had a stake in the outcome.

Taylor came away drained. Three years later, after contracting pneumonia, he was dead at the age of fifty-nine.

In 1919, the French poet Paul Valéry, looking out over a postwar Europe haunted by the ghosts of the dead and memories of mindless production in death's service, concluded a "Letter from France" by writing: "The world, which calls by the name of 'progress' its tendency towards a fatal precision, marches on from Taylorization to Taylorization."

Taylor was dead, but his system, and his sensibilities, lived on.

THE ERUPTION OF INTEREST IN SCIENTIFIC management in 1910 had fomented an efficiency craze that reached into home, farm and office as well as the factory. Its impact was heightened by the First World War, when the need to produce at levels once unheard of made Taylor's preoccupations those of the nation. Labor and capital were thrown into an unexpectedly intimate embrace. "From the bitterest sort of opposition to Taylor and all his works," Stuart Chase would write in *The New Republic* in 1925, much of organized labor now virtually embraced it. By 1929, in East Pittsburgh, Pennsylvania, the Westinghouse Electric and Manufacturing Company had a time-study staff of 120. At the United States Rubber Company, the International Harvester Company, the General Motors Corporation—the time and motion experts were everywhere. Something like a consensus had emerged that Taylor's methods represented the one best way to run a shop.

But not just the shop. In the late teens and 1920s scientific management split off into pieces and parts, factions, specialties, new disciplines, nascent social movements. One of Taylor's disciples, Henry L. Gantt, known for a system of critical-path scheduling using special charts, rounded up fifty engineers in a group he called the "New Machine." The group sought to establish an "aristocracy of the capable": engineers, efficiency experts and their friends would take the helm of society from know-nothing financiers and politicians. The New Machine proved short-lived, but out of it emerged a much broader technocracy movement, from which the word "technocrat" is derived.

William H. Leffingwell, a midwestern woodworker's son trained as a stenographer, applied scientific management to the office, experimenting with typists and clerks the way Taylor had with machinists and shovelers. There was one best way, he held, to insert paper into a typewriter, pin pages together or sit at one's desk—"well back in the chairs, with the feet placed squarely on the floor and head and shoulders erect." Leffingwell saw malingerers behind every file cabinet, just as Taylor did behind every lathe. He and his followers tracked how many minutes a day typists typed, fixed work standards of so many square inches of typed work

per hour and awarded bonuses to those satisfying them.

Efficiency reached into the physician's office and operating suite too. "Where could the rationality of business better be joined to the rationality of science," wrote one historian of medicine, "than in increasing the efficiency of the hospital?" Frank B. Gilbreth, a bricklayer turned contractor, had come under Taylor's influence in 1907. With his wife, Lillian, a psychologist, he adapted photography to root out unnecessary worker motions. (They and their twelve children inspired the popular book *Cheaper by the Dozen* and the film of the same name.) Frank later went into the operating room himself, observing dozens of operations. "If you were laying brick for me," he told one surgeon, "you wouldn't hold your job ten minutes." Medical journals began carrying articles such as "'Efficiency Engineering' in Pelvic Surgery: One- and Two-Suture Operations," which told how to save time and motion through better suturing technique and operating-room organization.

By the late 1920s it had begun to seem that all of American society had come under the sway of a single commanding idea—that waste was wrong, that efficiency was the highest good and that eliminating one and achieving the other was best left to the experts. The 1928 election of a mining engineer, Herbert Hoover, secretary of commerce in the Harding and Coolidge administrations and author of the influential report *Waste in Industry,* brought scientific management into the White House itself.

> *"If you were laying brick for me," Gilbreth told one surgeon after an operation, "you wouldn't hold your job ten minutes."*

Almost from the very beginning, Taylorism spread around the world. Within a few years of its American publication, Taylor's most popular work, *The Principles of Scientific Management,* had been translated into Chinese, Dutch, French, German, Italian and Russian. Mussolini embraced scientific management. So did Lenin and Trotsky. During the Weimar years, between the end of the First World War and the rise of Hitler, German *Rationalisierung,* or "rationalization," set out to fuel the entire national economy with order, system and efficiency. The aim was to bring together in a single heroically scaled idea both *Taylorismus* and the assembly-line techniques represented by *Fordismus.*

Among Taylor's foreign students were the Japanese. Yukinori Hoshino, a bank director from Osaka, was visiting the United States in 1911, when scientific management was much in the public eye. He sought and received permission to translate one of Taylor's books, which was published in Japan in 1913. Soon Japanese students, industrialists and educators were making the pilgrimage to Taylor's estate and touring his showcase companies. Japanese shipyards, cotton mills and government factories launched time studies and other experiments in scientific management.

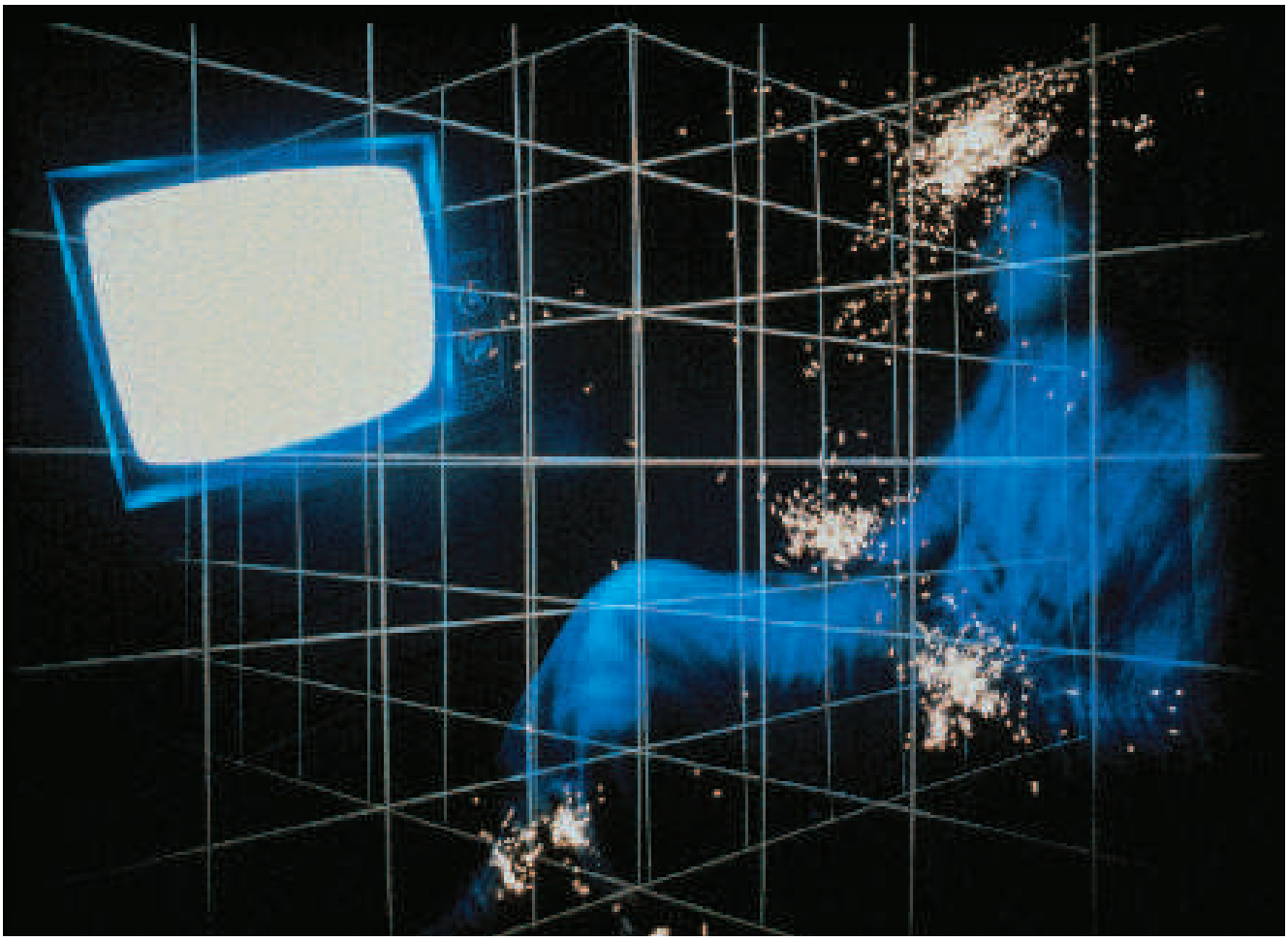
In 1923 the Mitsubishi Electric Company reached a technical cooperative agreement with Westinghouse to send people to the United States to learn time-study methods. The delegates from Mitsubishi analyzed hundreds of the tasks involved in the manufacturing of electric fans and soon were spreading the new techniques throughout Japan. And Taylor's disciples visited Japan, to lecture, to inspect factories and otherwise to help guide the embryonic movement. In 1961, when Taylor's son Robert visited Japan, executives of the Toshiba Corporation implored him for a pencil, a picture, anything that had been associated with his father. "They wanted to feel or touch," he wrote, "something that Fred Taylor had touched or handled."

As Taylorism touched each of the world's industrial nations, the story was never quite the same, yet never altogether different: first the thrill among a few people smitten with Taylor's ideas; then letters back and forth to the United States; translation and publication of Taylor's writings; industrial experiments; a swirl of controversy; some form of institutionalization, and finally the spread of Taylor's ideas.

Of the two great American industrial movements, Taylorism and Fordism, Taylorism was probably the more all-encompassing. As the political scientist Judith A. Merkle of Claremont McKenna College in Claremont, California, has pointed out in *Management and Ideology,* Taylorism, compared with Fordism, has an "immense advantage in its ability to absorb new technologies and to adapt itself over time." The assembly line can be likened to a biological species adapted, through evolution, to its own peculiar ecological niche, like a Galápagos tortoise. Scientific management, in contrast, adapts the way a virus does, fitting in almost everywhere. In the words of one reporter, Taylorism was a "machine of universal efficiency."

Taylor saw knowledge, not muscle power, as the prime productive resource; today the "knowledge industry" is looked to as the source of most new jobs, whereas good blue-collar jobs that blend head and hand disappear. Robert B. Reich, the former secretary of labor in the Clinton Administration, lays the divorce of brain from brawn squarely at Taylor's feet, adding: "One cannot overstate the importance of this split to the way America organized itself." In the 1940s, when a labor union commissioned a study of Taylorist time-study practices, its author, William Gomberg, pictured a *Brave New World*–like future in which "the simplification of jobs at one end of the job-rating scale and the increasing demands for skills at the other end would soon create a society in which only the geniuses and morons would survive."

The coming of the computer has extended Taylorist sensibilities even further; computer programs embody the very split between thinking and doing that is the hallmark of Taylorism. More and more, work bifurcates into two streams—skilled programming, planning and analytical work at the top, and low-skilled program execution, in its various guises, at the bottom. Engineers, economists, planners and systems analysts extract the last fraction of a cent from a fast-food hamburger at one end, while legions of minimum-wage drones peck at cash register touch screens at the other.



*Mike Mandel,* Watching TV, *1987*

Today Taylorism is at least intellectually out of fashion, and few admit sympathy with its precepts. In 1986 the Japanese industrialist Konosuke Matshushita predicted that the United States would lose in the race for international markets because it is infected with the disease of Taylorism, with its disinclination to tap the flexibility and intelligence of the average worker. When John Sculley, then the chairman and chief executive officer of Apple Computer, spoke at then-President-elect Clinton's economic conference in Little Rock before the inauguration in 1993, it was Taylor, along with Henry Ford, whom he invoked to represent the heavy hand from which the American economy must free itself.

AND YET, EVEN AFTER MUCH-BRUITED attempts to bring participatory democracy to the workplace, Taylorism survives. A manager at the automobile factory jointly operated by the General Motors Corporation and the Toyota Motor Corporation in Fremont, California, pinned its recent success squarely on "the intelligent interpretation and application of Taylor's time-and-motion studies." And in *White-Collar Blues,* the labor-relations expert Charles Heckscher of Rutgers University in New Brunswick, New Jersey, points to "a paradoxical reversal" in the modern workplace: For all the "effort to draw out the good will of blue-collar workers, middle managers are being treated increasingly as cogs in the machine." What's this, he says, but "a kind of Taylorization of management."

In Taylor's vision, man and machine work together like clockwork. In that vision lies the great paradox of modern life. Every day we reap the material benefits of the cult of workplace efficiency he championed; yet we chafe—we scream, we howl—at the psychic chains in which it grips us. When young people in the 1960s sniped at the System, it was in part the Taylor system itself, institutionalized in corporate America, that they opposed. It was Taylor, after all, who first wrote in 1911, explicitly and without apology:

"In the past the man has been first; in the future, the system must be first."

And, one might argue, it is. ●

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# DOLLARS AND ANTISENSE

*The fortunes of an industry, and a new generation of drugs, ride on a clever form of synthetic DNA*

BY SUDHIR AGRAWAL

CALL IT A CHRISTMAS truce—the effect is the same, even if the calendar says late spring. This May a few veterans of the biotechnology invasion, many of them old friends or former colleagues, are emerging from gleaming bunkers worldwide to exchange news, share a few pleasantries and then march back to the trenches. The official occasion is a conference in Cambridge, Massachusetts, gathering the leading lights in one of the most exciting fields in genetic research: antisense technology. But the meeting may stick in the mind more as a moment of rare calm, when the air cleared after an era of entrepreneurial and scientific fireworks, and we briefly counted our victories and our losses.

*Lawrence Fane,* Sanctus, *1994*

Since the early 1980s dozens of biotechnology concerns have taken root along the streets that surround the Massachusetts Institute of Technology in Cambridge, a perennial seeding ground for start-up companies. Most of the early biotechnology firms were just small gangs of daring investigators whose eureka ideas launched them out of academia and into the business world. They came from Harvard Medical School, its affiliated hospitals, and numerous surrounding campuses, as well as MIT. They seldom had much business sense, laboratory space or financial backing, especially compared with the pharmaceutical giants with whom they aimed to compete. What they did have were grand dreams of novel compounds derived from revolutionary discoveries in molecular biology.

The new biotechnologies held the promise of novel therapies for hard-to-treat diseases. They pointed toward more effective drugs with fewer side effects than traditional pharmaceuticals, most of which were developed through a hit-or-miss approach and often attack the entire body to stop a disease. Biotechnology, on the other hand, would provide therapies capable of pinpoint accuracy—therapies that could diffuse through the body like antiterrorist squads, striking trouble spots but leaving their surroundings untouched.

Like most invasions, however, this one was a messier business than any battle plan could suggest. It soon became clear that even the most brilliant idea for a new drug needed patience, tremendous capital and continual refinement to weather the complex, competitive drug-development process. As small companies stumbled, they were gobbled up by the dozens by other companies or were drastically downsized as investors lost heart. In 1987, when biotechnology hype was at its most inflated, 119 new biotechnology companies were founded. Then came the inevitable pinprick. Positive clinical results came too slowly, and there were many notable disappointments. In the early 1990s, for instance, three biotechnology compounds targeted at sepsis—a bacterial infection that is one of the top ten causes of death among the elderly—bombed one after another. In the first half of 1994 only thirteen new biotechnology companies were founded; during that same period of time the amount of equity financing for biotechnology companies fell from $525 million to $124 million, according to the accounting firm Ernst & Young LLP.

A few companies managed to safely shepherd their drugs to "clinicals"—industry jargon for the human clinical trials that are the ultimate proving grounds for new drugs. But the trip was often more free fall than free enterprise. As some nervously joked: biotechnology is like bungee jumping, only without the bungee.

TODAY, SOME OF THE MOST NOTABLE SURVIVORS of the biotechnology shakeout have prime real estate in Cambridge. Across and up the Charles River from my office at Hybridon, Inc., a gleaming, cathedral-like structure of brick and glass looms above the Massachusetts Turnpike. There, a biotechnology old-timer called Genzyme Corporation manufactures a new drug

for a rare genetic disorder called Gaucher's disease. Also in Cambridge you can find biotechnology stars such as Vertex Pharmaceuticals Inc., which makes a hot new protease inhibitor now being tested against the human immunodeficiency virus (HIV) in phase III clinical trials (the final stage before a drug is approved for the market). Nearby Biogen, Inc., just last year launched a treatment for multiple sclerosis—only the second such drug to reach the market.

If the biotechnology boom continues, it is triggered, in large part, by the sparks thrown off by genetic research. Every gene sequenced by private companies or as part of the Human Genome Project becomes a new target for drug companies, large and small. Millennium Pharmaceuticals, Inc., in Cambridge, recently made headlines by discovering a putative fat-causing gene in mice.

The successes of the surviving companies is a sign that the biotechnology industry is maturing. And antisense technology seems to hold special promise. In a period of only ten years or so, about a dozen antisense-based drug candidates have made it to clinicals. Antisense technology is both simple and wide-reaching: it uses synthetic copies of the basic components of life—the nucleotides that make up DNA—to block disease processes at their origin. And it builds on some of the fundamental tenets of modern molecular biology.

PART OF THE POWER OF ANTISENSE RESTS ON the fact that the genetic code of every known organism is made up of the same handful of nucleotides—the four-letter chemical alphabet that, when combined into a sequence called a gene, tells a cell how to make a specific protein. And proteins guide the growth, development and death of each organism. Almost all diseases occur when a mutated gene is transcribed into a "bad" protein, when a gene pumps out too much or too little of a given protein or when the genetic code of a microorganism or a virus codes for proteins that cause disease.

The path from DNA to protein synthesis begins in a cell's nucleus, when the double-stranded DNA helix unzips itself from one point to another—typically the length of a single gene. A compound chemically similar to DNA, but single- rather than double-stranded, is then synthesized, letter by chemical letter, from one of the strands of the unzipped DNA. Known as mRNA (the "messenger" variety of the molecule known as RNA), it is a biochemical carbon copy of the original DNA strand.

Ordinarily, mRNA leaves the nucleus and floats off into the cytoplasm, where it becomes the physical template for protein synthesis in the cell. If you keep it from forming, however, or somehow jam its genetic signals, the protein it encodes cannot be synthesized. Hence one obvious way to prevent a "bad" protein from forming is to block the mRNA strand that codes for it. That can be done by building a compound that would bind to the strand, just as the mRNA strand naturally binds to its complementary strand of DNA. (Because mRNA is known as the "sense" strand that helps form protein, its synthetic complement is known as "antisense.") Such compounds may help stop many protein-related illnesses.

As investigators gradually unraveled the steps in protein synthesis, they began to realize that antisense might be an

*Louise Nevelson,* Young Tree VI, *1971*

ideal agent for new drugs. Drug designers usually target their efforts against proteins rather than protein templates. The trouble is, once protein synthesis begins, millions of copies of a given protein can be churned out—all of which have to be destroyed or deactivated. Drugs that can eliminate such proteins take years to design and usually attack other proteins as well, thereby causing unwanted side effects.

How much mRNA of a given type is produced depends on the gene that codes for it. But compared with the protein it produces, the amount of mRNA is trivial. If a drug blocks mRNA rather than a protein, therefore, it has a much easier job ahead of it. Such antisense drugs have the added advantage of specificity: by blocking the synthesis of one, and only one, protein, they are less likely to cause side effects.

THE BIRTH OF ANTISENSE SCIENCE OWES A great deal to the molecular oncologist and biochemist Paul C. Zamecnik, the founder of Hybridon. Zamecnik is one of the towering figures in molecular biology, the winner last year of the first Albert Lasker Award for special achievement in medical sciences. At eighty-four years of age, he still conducts experiments with his wife and laboratory partner, Mary, who studied under the late Danish cell biologist Albert Fisher.

Zamecnik's first great discovery came in the early 1950s, when he and coworkers at Massachusetts General Hospital in Boston showed that proteins are manufactured by a structure within the cell called the ribosome. The ribosome, Zamecnik explained, helps translate the strand of nucleotides in mRNA into a sequence of amino acids. (Each group of three nucleotides, known as a triplet, codes for one amino acid; a linear strand of amino acids, or polypeptide chain, forms a protein.) Investigators could then identify specific steps in protein synthesis that drugs could target. For example, if a strand of mRNA never reaches the ribosome, they now knew, the protein the mRNA codes for is not made.

Zamecnik's next major discovery essentially launched the science of antisense. By the 1970s molecular biologists were fascinated with organisms known as retroviruses, the best-known examples of which are HIV and feline leukemia virus. The genetic information in such viruses is carried on strands made up of the same nucleotides found in mRNA. Indeed, the virus itself is essentially RNA with a protective coat of protein and fat. Once inside the cell, a retrovirus converts its RNA into DNA, which it fuses into the host cell's genome. The host's own replicative machinery, which faithfully but blindly obeys its DNA, then mass-produces copies of the viral genome and proteins.

It is a devilish process, because host cells must essentially be shut down or destroyed to stop the virus from reproducing. Failing that, one would somehow have to mute the rogue genetic sequence the virus has planted in the host DNA. That is exactly what Zamecnik did.

In 1978 Zamecnik and Mary L. Stephenson, a longtime associate at Massachusetts General Hospital, added about a trillion strands of synthetic DNA, each thirteen nucleotides long, to a culture of chicken cells. Both the sequence and length of the compound guaranteed that it would bind only to viral mRNA that coded for a chicken retrovirus known as Rous sarcoma. When the synthetic DNA bound to the viral mRNA, they found, mRNA was not translated into protein. The virus still lurked in the host cell's genome, but it could no longer make copies of itself. It had been disarmed.

Suddenly retroviruses, so long resistant to any therapy, seemed treatable. And if so, perhaps other diseases could be treated by similar tactics. Unfortunately, the path to cures was anything but clear. Making synthetic antisense was extremely difficult, for one, and it involved relatively undependable chemical reactions. Zamecnik's lab needed six months just to make antisense in the microgram quantities needed for the retrovirus experiment; making enough of it for the lengthy laboratory, animal and human trials needed to prove a drug's safety, efficacy and dosage would have been impractical.

Given such technological hurdles, Zamecnik did little antisense research for several years. Molecular biology, meanwhile, continued to advance at a blinding pace. By the late 1970s, the biochemists Walter Gilbert of Harvard University and Frederick Sanger of the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, had developed two revolutionary (and complementary) methods for sequencing DNA. (As it happens, Zamecnik was sequencing the Rous sarcoma genome at Massachusetts General Hospital at about the same time Gilbert was developing his new method across the river at Harvard. Zamecnik and his colleagues needed three years to sequence twenty-one nucleotides; Gilbert sequenced 101 nucleotides in six weeks.)

Sanger and Gilbert's work dovetailed with the development of automated DNA synthesis by many other investigators. By 1984, thanks to advances in hardware and software, investigators could simply punch a nucleotide sequence into a machine, and the machine would synthesize the sequence.

With the development of synthetic DNA, the basic strategy of antisense therapy finally became feasible—or at least testable, and Zamecnik renewed his study of it, con-

centrating on HIV. In 1984 his laboratory began to collaborate with the molecular biologist and co-discoverer of HIV, Robert C. Gallo, who was then sequencing the genetic code of HIV at the National Cancer Institute in Bethesda, Maryland. Two years later, Zamecnik and his colleagues reported that antisense had been directed against HIV in cell culture for the first time and had significantly reduced viral replication. Prompted by those results, Zamecnik called his old friend and former labmate Daniel M. Brown, also at the Medical Research Council in England, and asked him to suggest new recruits for antisense research. Brown referred him to me.

In the late 1970s I had worked in India on DNA synthesis, then continued that work in England with Brown's colleague Michael J. Gait, a pioneer in the field. When I joined Zamecnik in 1987, my job was to show that synthetic antisense could be made stable in small animals and, subsequently, in people. But my duties soon expanded dramatically.

The period from the mid-1980s until the early 1990s was the heyday of biotechnology start-ups.

*Richard Deacon,* Back of My Hand, No. 7, *1987*

In 1989 Zamecnik joined in, forming Hybridon, and just a year later I became the company's principal research scientist. We were a cozy group, with three scientists, two technicians and two laboratories that took up 2,000 square feet of a building in Shrewsbury, Massachusetts. Today, Hybridon has 196 employees. Sixteen scientists work in my laboratory alone, and we occupy more than 10,000 square feet of the 91,000-square-foot building that serves as our headquarters.

BIOTECHNOLOGY COMPANIES ARE PRIMARILY research engines, and so former academics often find them more congenial than established pharmaceutical firms. (Research in the latter shares pride of place with marketing, manufacturing, dealmaking and entrepreneurship.) Still, some culture shock remains for academics who make the switch to for-profit biotechnology, and financing is a continual concern. For instance, the "burn rate," or amount of cash a company needs to survive a month, has increased dramatically over the years. In 1995, according to Ernst & Young, only about half of all biotechnology companies had enough cash on hand to survive for two more years.

Investor confidence is built on successful experimental results, and those take time. Luckily, many of the answers to the early challenges faced by antisense technology were relatively easy to meet.

Our first challenge was a fundamental one. Some investigators doubted that molecules as large as a synthetic antisense strand could enter a cell. Fortunately, many early test-tube experiments had confirmed what Zamecnik and Stephenson found in their retrovirus study: antisense molecules can indeed penetrate the cell membrane.

The next hurdle was more complex. Antisense strands may flit about freely in a test tube filled with cells, but when the strands are introduced into the body, they fall prey to enzymes that attack invaders. To breach such natural defenses, viruses have had to come up with diabolically clever ways to mask and protect their naked strands of nucleic acids.

The weak link in our approach, we quickly realized, was the biochemical "backbone" that joins the nucleotides together in a strand. That backbone was relatively vulnerable to the body's enzymes. Fortunately, studies done more than twenty years ago suggested that the backbone could readily be reinforced: one of the oxygen

atoms along the slender chain simply needed to be replaced with a sulfur atom. That single chemical substitution would be enough to protect the antisense strand from a premature death.

Thanks to the first generation of reinforced antisense, investigators have been able to study antisense compounds in living organisms, rather than just in test tubes. The results have been both inspiring and educational. In the past two or three years many groups have blocked specific genetic sequences with antisense. In Europe a group of Swiss and German investigators has shown that antisense can reduce the amount of hepatitis B virus in the livers of infected ducks. At the National Cancer Institute, investigators have found that antisense can keep down the production of a tumor-related enzyme known as protein kinase A and thereby stop the growth of human tumors implanted in mice. And in Japan, a group has used antisense to target a gene linked to high blood pressure in rats.

*A few years ago we could make only thimblefuls of DNA, for about $10,000 a gram. Today we synthesize it by the bucketload, for $200 a gram.*

Those and many other reports have dispelled much of the doubt about the therapeutic potential of antisense. Part of the skepticism arose from the vast difference between what specialists in the field knew about antisense and what the general scientific community knew about it. In the early days of antisense research, many newcomers to the field expected to produce dramatic results easily with such "miracle" compounds. Few bothered to delve into the intricacies of antisense, however, and they often worked with off-the-shelf antisense strands that were either of poor quality or inappropriate for a given study. As a result, the field was cluttered with junk science—reports suggesting that antisense compounds are inactive or have completely unexpected effects. That early impression has taken years to clear away, and it still lingers in some circles.

Part of the housecleaning included establishing guidelines for how antisense must be handled, and of what quality it must be, in order to do its work. More than any other trend, however, advances in sequencing the genomes of natural organisms have bolstered antisense research. Genetic landmarks have been established from one end of the human genome to the other, many stretches of DNA between those landmarks have been sequenced and thousands of genes have been identified. Meanwhile, the genetic codes of simpler organisms such as yeast and *Escherichia coli* bacteria have been sequenced in their entirety [see "Chain of Being," by Howard Bussey, *The Sciences,* March/April 1996].

Once the sequence and function of a gene are known, the gene becomes a target for many therapeutic approaches. One of them is antisense; another is so-called gene therapy, in which new DNA is introduced into a host cell's genome to override a malfunctioning gene or replace a missing one. Antisense studies, in turn, shed further light on a gene's function by blocking the gene's activity within the organism. At a recent neurobiological conference in Oxford, England, for instance, several investigators told of using antisense to see how genes influence behavior and other neural activity. The investigators simply targeted mRNA transcribed from a gene in an animal's brain, blocked its activity and then noted whether the animal behaved differently.

Propelled, in part, by the welcome breeze from genome research, we had relatively smooth sailing through our early experiments with rodents. But antisense had more obstacles to overcome before it could be studied in animals more closely related to people. The compounds had to be made stable enough, for instance, to last longer than a few hours or a few days in the body. But when we injected monkeys with our first strands of stabilized antisense, the animals fell ill and a few of them died. Although it was only the first time we had observed the effects of modified synthetic DNA in a primate, the monkeys' reactions still took antisense investigators by surprise.

It turned out that by swapping an oxygen atom with a sulfur atom in the antisense backbone, we had inadvertently created a compound that, at high doses, activated a part of the immune system known as complement, thereby triggering potentially fatal changes in heart rate and blood pressure. Fortunately, we have since been able to prevent such immune reactions—in monkeys as well as people—by slowly administering the compound intravenously, or by injecting it under the skin or in the muscle, rather than injecting it directly into the bloodstream all at once.

In the past few years such insights and improvements have helped biotechnology companies identify a host of attractive targets for antisense drugs. Isis Pharmaceuticals, Inc., based in Carlsbad, California, has announced positive results in human trials of a drug designed to treat Crohn's disease, an inflammatory bowel disorder. Lynx Therapeutics, Inc., in Hayward, California, and Genta, Inc., in San Diego, California, are developing antisense compounds targeted at cancer and restenosis—the "renarrowing" of arteries that have been unclogged by angioplasty. And two investigators at East Carolina University in Greenville, North Carolina, are developing an antisense treatment for asthma, which has already shown promising results in rabbits.

In 1993 Hybridon's anti-HIV compound became the first antiviral antisense drug given directly to patients. (Although many therapies exist for HIV, there is still a tremendous need for new drugs, particularly because the virus may develop a resistance to current drugs and some patients cannot tolerate them.) Early clinical trials, overseen by R. Russell Martin, have shown our drug to be safe even at the highest doses we have given. More encouraging still, when some patients were treated for only eight days, the amount of virus that infected white cells in their blood decreased by as much as 90 percent. That finding is being confirmed in a second trial in which patients are being treated for longer periods of time.

Last year Hybridon also began human trials of an anti-

sense drug that targets cytomegalovirus (CMV). (Isis is testing a CMV drug of its own.) In most cases CMV is as benign as it is ubiquitous, but in people with an immune-system dysfunction of the kind caused by HIV, it can cause serious problems, including blindness. Our drug includes new modifications to the nucleotide backbone that make it even more resistant to degradation by enzymes in the body. As a result, this "second generation" synthetic antisense should stay active in the body longer than any of its predecessors.

Of course, we are all still refining our tactics. The first antisense therapies, for instance, had to be given by injection, since the compounds degraded when taken orally. One of Hybridon's greatest successes came in 1995, when we showed that antisense compounds could reach their targets intact even when taken as a syrup—a far more practical delivery method than injection. In recent studies in which antisense was made to target human tumors implanted in mice, our oral formulas slowed tumor growth just as effectively as injections of the drug.

Because every DNA molecule is synthesized from just four nucleotides, any kind of antisense—any strand of DNA—can be made from the same set of chemicals. That fact, and dramatic advances in technology, imply that the new drugs can now be manufactured by machine with relative ease. A few years ago we could make only thimblefuls of DNA, for about $10,000 a gram. Today synthetic DNA can be manufactured by the bucketload, and it costs only about two hundred dollars a gram.

TEN YEARS AFTER ITS TUMULTUOUS BEGINnings, the biotechnology industry has come to a critical juncture. The list of new drugs being developed is impressive, and even small biotechnology companies are now sequencing key genes and inventing new ways to screen and manufacture compounds. But the only true gauge of success, in our industry, is a human clinical trial. In the past few years any number of compounds have cruised through early trials only to founder when given to people. The sepsis drugs, for instance, seemed poised to take over a $1 billion drug market, only to fail in their phase III trials, crippling investor confidence.

The survivors of the biotechnology invasion—including two of the three companies whose sepsis drugs failed—have grown tougher, more cautious and more deeply entrenched over the years. Because antisense investigators design their drugs for specific targets rather than simply synthesizing scattershot compounds, they may be less likely to suffer ugly setbacks. Moreover, when failures do occur—such as the unexpected deaths of our monkeys—they tend to point to effective corrective action. And so the work continues, with a handful of innovators giving way to legions of employees, and flimsy offices abandoned for sprawling edifices—until the scrappy, daredevil companies of a few years ago inevitably begin to resemble the pharmaceutical giants they once had the temerity to challenge. ●

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*Christopher Bucklow,* Sleeping Guest (L.G.) 8:11 P.M. 12-7-96, *1996*

# PULLING TEETH

*Can t live with em, can t live without em*

PHOTOGRAPHS BY ROSAMOND PURCELL

*Rosamond Purcell,* Elephant's Molar, *1995*

WE DEFINE OUR OWN CLASS OF VERTEBRATES BY THE GROWTH OF AN internal skeleton (while insects and many other invertebrate groups form their protective hard parts on their outsides). And we tend to be fascinated by what we cannot usually see, yet recognize as essential. Thus we take delight in X rays of our own invisible interior, experience a special horror if bone accidentally breaks through skin, and symbolize the macabre as a dance of articulated skeletons. Yet we rarely realize that one important part of our skeleton, representing the oldest structures of all by evolution, stands readily exposed to daily scrutiny and attention—our teeth. Ya gotta eat.

But necessary exposure implies inevitable risk. Our bones are cushioned, but our teeth are vulnerable to all the slings and arrows (and fists, sidewalks and hockey pucks) of the world's outrageous fortune. Modern dentists possess an armamentarium of sophisticated devices for preservation and salvation. But their forebears could do little more than follow literally the prescription that Jesus gave (metaphorically, I trust) as treatment for a wandering eye (in a man with an adulterous heart) in his Sermon on the Mount: "if [it] offend thee, pluck it out, and cast it from thee, for it is profitable for thee that one of thy members should perish, and not . . . thy whole body."

As one of the few routinely successful forms of old-time surgery, and as a crude and unpleasant way to save many lives that would otherwise have been lost to spreading infection, the yanking of teeth became an obvious butt for humor—as shown here both in the elegance of eighteenth-century Meissen porcelain, and in a background print of the same age and activity. (I don't imagine that the Meissen folks crafted many scenes of gangrenous death on the battlefield or birthing room, where surgery could do little and medicine usually made matters worse.) Nonetheless, as depicted in both print and porce-

lain, the subjects were not amused; "like pulling teeth" remains our standard metaphor for necessary things done with great reluctance.

Nonhuman mammals often face a precisely opposite dental problem—an upper limit set to life because teeth can neither be removed nor replaced. Non-mammalian vertebrates (including sharks as a primary example) can often replace worn or broken teeth almost indefinitely. But we mammals pay a price for each supposed gain in adaptation. Mammals have evolved complex teeth, requiring delicate and precise occlusion between upper and lower members in chewing. Good occlusion implies permanent positioning, so mammals must give up the conveyor-belt system of continuous replacement used by fishes and reptiles with simple pointed teeth, and settle instead for only two sets—"baby teeth" for the small juvenile jaw and a single adult set for later life.

*Rosamond Purcell,* Der Zahnbrecher, 1741, *1995*

In Darwinian nature, life may generally be nasty, brutish and short, but some mammals survive to die of old age. Ironically, the most common cause of such "programmed" death is the wearing down of irreplaceable teeth to decrepitation. Ya gotta eat.

Adult elephants have no potent nonhuman predators. Their large and elegantly complex molar teeth—shown in surprising scale in Rosamond Purcell's photograph—do not follow the usual mammalian rule. Only one molar can fit on each side of the jaw at a time—giving four molars in toto at any moment. A worn-down molar can be discarded and another emplaced (whereas most adult mammals sport all their molars, usually two or three for each side of each jaw, as permanent fixtures). But after the last elephant molar is emplaced and worn down, no substitutes remain, and a toothless old animal may starve to death.

How ironic, then, that modern elephants are not threatened as a species by this natural form of dental distress, for all elderly animals must eventually die. Elephants are vulnerable because we have imposed upon them, for rapacity rather than relief of distress, the uniquely human strategy of pulling teeth. We kill them to extract their incisors for ivory. ●

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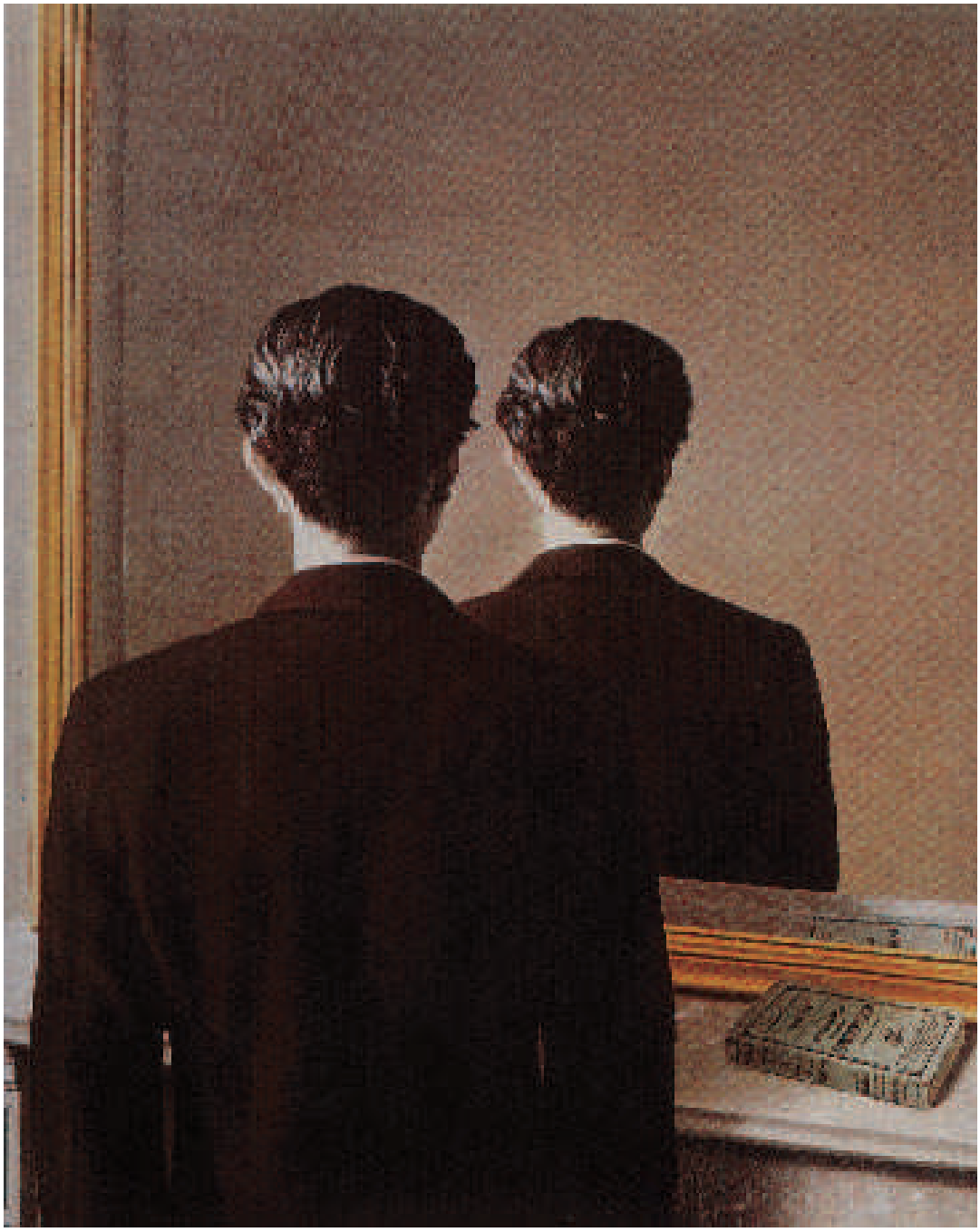
# Through the Looking Glass

*In arithmetic, 5 and 7 can be added in any order to yield 12. When order does matter, you have entered the strange, disorienting world of noncommutativity.*

BY DANA MACKENZIE



*René Magritte,* La Reproduction Interdite, *1937*

IT IS THE YEAR 2025. THE DIREST PREDICTIONS of global warming have come to pass, and you, along with millions of other sunburned Yankees, are fleeing to the far north. Stopping in a likely looking boreal boomtown, you learn that the Yukon Land Company is selling land at a price of $1,000 for a one-twentieth-acre plot or $2,000 for a one-tenth-acre plot. Fair enough, you think. Then you glance across the street, where a huge crowd is milling around in front of a garish holographic sign:

The Kon-Yu Land Company welcomes YOU!!
Buy from us and get a FREE BONUS!
Kon-Yu s Price: $1,500 per 1/15 acre
** PLUS **
Free Ice Cream Maker!!!

You could certainly use some homemade ice cream. And, after all, other things being equal, why not? You step toward the excited throng.

And then, prompted by some intuition, you reach for your pocket calculator. A few quick keystrokes are enough to convince you that the huddled masses across the street are making a big mistake. If 1/15 were indeed the average of 1/10 and 1/20 (as the crowd apparently assumes it is), $1,500 would be a fair price for a Kon-Yu plot. But it is not. One-fifteenth is about 0.067; the mean of 1/10 and 1/20 is 0.075. The rubes are overpaying by a cool 12 percent! In mathematical terms, they have forgotten that, in general, the average of the reciprocals of two numbers is different from the reciprocal of the average. The operations "take the average" and "take the reciprocal" do not commute.

My dystopian fable might be far-fetched, but the flaw in reasoning that it illustrates is extremely common. In years of teaching freshman calculus courses, I never ceased to be amazed by how many of my students' mistakes boiled down to problems with commutativity. Put the expression $(x + y)^2$ on an exam and, as ineluctably as boats spiraling into a whirlpool, even some students who know better will expand it as $x^2 + y^2$—as if the rules of arithmetic let them add or square numbers in either order.

What is the source of that fatal allure? Much of it, I suspect, stems from a faulty analogy. Early in primary-school arithmetic class, children learn that when they add two numbers, the order does not matter. It is understandable that years later, grappling with more complicated expressions and working under time pressure, students' minds may default to that familiar commutative law.

Yet it is also a peculiar thing to do. After all, nobody takes commutativity for granted outside the classroom. When you get dressed in the morning, it may not matter much whether you put on your watch before your shoes or the other way around: "put on watch" commutes with "put on shoes." "Put on *socks,*" however, does not, and even small children know which order of operations is likely to yield more satisfactory results (though they may vary the order anyway for fun). Similarly, woe unto the poor soul who, when making hot chocolate, inverts the operations "heat milk in microwave oven" and "stir chocolate powder into milk." Heating the milk first yields a creamy treat; adding the powder first, a lumpy mess—as I once discovered the hard way.

In mathematics the rule of thumb is that numbers commute but operations or actions generally do not. The second half of that formula, the noncommutativity of actions, is a little-known touchstone of mathematics, with implications ranging from the trivial to the profound. In many cases it injects a spark of anarchy into a tame, well-behaved theory (just as it played havoc with the expectations of Kon-Yu's customers). In other guises it keeps turning up, like a theoretical Forrest Gump, at the scene of major upheavals in the mathematical world view. Noncommutativity underlies the perplexities of quantum mechanics, including the famous uncertainty principle of the German physicist Werner Heisenberg. In recent years the subject has burst free of its roots in algebra and has given rise to a radically new kind of geometry, which might give physicists their next big boost toward a grand unified "theory of everything."

**WHAT IS COMMON *to the perplexities of putting on your socks, tying your shoes and quantum mechanics? Noncommutativity.***

IN LEARNING TO APPRECIATE NONCOMMUTATIVity, you first need to know that not all noncommutative operations are alike. That may sound odd—after all, things either commute or they do not, right? Not exactly. Consider two ships that start out side by side at the equator. One ship sails 100 miles east, then turns and sails another 100 miles north. The second ship sails 100 miles north, then 100 miles east. Do they end up in the same place? No; the second ship will end about one-thirtieth of a mile east of its sister. If the ships had sailed ten times farther in each direction, the discrepancy would have been about thirty-two miles—nearly 1,000 times greater. Commutativity fails because the earth is curved, and the extent of the failure depends on the actions the ships take.

The failure of commutativity becomes strikingly clear when applied to the mundane task of untying knots. Twenty-three centuries ago Alexander the Great vented his impatience with that task by slicing asunder the legendary Gordian knot. Today mathematicians continue to hatch surprising improvements on Alexander's brute-force approach. John Horton Conway of Princeton University [see "Mathemagician," by Charles Seife, *The Sciences,* May/June 1994] has harnessed the noncommutativity of actions to create an ingenious method for untying knots without swordplay.

Conway tackled a kind of knot called a tangle, which he defined as any mess of string with four ends. For convenience he assumed that those ends always fall on the four vertices of a square. The goal is to unknot the two pieces of string in such a way that they end up lying parallel to each other along the top and bottom of the square, like the bars of an equal sign: =. Conway proved that, for an important class of tangles called the rational tangles, you can reach that goal through two simple operations. The first operation is *turn:* take the entire lump of string and rotate it ninety degrees clockwise. Suppose the ropes are still side by side

but vertical: ‖. Then one turn gives rise to the = sign. If you turn again, you get back the original ‖ sign. (The strings have changed places, but because the tangle looks like the original one, it is considered the same. In general, two tangles are considered equivalent if you can change one of them into the other by moving the strings around inside the square formed by the ends. But if you move an end or pull a loop over one of the ends, you might create a different tangle.)

Conway's second operation can be called *twist*. Take the tangle and—without moving the leftmost ends of the string—give the rightmost ends a twist that puts the top string over the bottom. If you twist the = configuration, you create an X-shaped tangle in which the string that starts at the top left passes over the one that starts at the bottom left (an overpass, if you will). If you twist the ‖ tangle, you get the ‖ tangle again. It is easy to see that the operations *turn* and *twist* do not commute. In fact, if you take the = tangle, turn it and then twist it, you get the ‖ tangle. If you twist first and *then* turn, you get an X in which the string that starts at the top left crosses under the other one: an underpass.

*A –3/5 tangle*

CONWAY DISCOVERED a way of describing the number of twists in a tangle by a single number. Since the = tangle has no twists in it, its Conway number is zero. To compute the Conway number of more involved tangles, just add one for every twist. Thus the operation *twist* on tangles corresponds to the operation "add one" on numbers. (If you wanted to, you could also subtract one by doing an "untwist.")

What about the operation *turn?* At first glance there seems to be no reason that moving a knot around should change the number of twists. Here is where Conway had an astounding insight: in fact, rotating a tangle corresponds to taking the negative of the reciprocal of the number of twists. For example, if you give a turn to a tangle with three twists, the resultant tangle is considered to have negative-one-third twist in it (a Conway number of –1/3).

Outrageous? Yes, but, amazingly, it works. Take the zero tangle, carry out any sequence of twists and turns you like, and the resultant tangle will have a Conway number. That number will be a fraction, positive or negative. A little thought will convince you that, by appropriate twisting and turning, you can generate any fraction you can name. (In some cases you end up dividing by zero. That is why the ‖ tangle, as you might guess, has a Conway number of both plus and minus infinity.) Because mathematicians refer to fractions as rational numbers, tangles created by twisting and turning are called rational tangles.

To untie any rational tangle, all you need to do is apply any series of operations that reduces the Conway number to zero. Like magic, the strings will return to the = position. In lectures, Conway demonstrates his technique by producing two lengths of rope and leading four volunteers through an arithmetic square dance. You might prefer to experiment with shoelaces. Whatever your equipment, consider the tangle illustrated on this page (Conway number: –3/5), which results from the sequence *twist-twist-twist-turn-twist-twist-turn*. You could untie it by an appropriate sequence of "untwists" and "turn backs"; or you could forge ahead as follows: *twist* (–3/5 + 1 = 2/5), then *turn* (–1 divided by 2/5 = –5/2), then *twist* three times (–5/2 + 3 = 1/2), *turn* (–1 divided by 1/2 = –2), and *twist* twice more (–2 + 2 = 0). Try it!

Conway's method works because the physical manipulations of twisting and turning exactly mirror the arithmetic operations involved in calculating the Conway number. In other words, the operations *twist* and *turn* fail to commute, and the operations "add one" and "take the negative reciprocal" fail to commute in exactly the same way. That parallelism gives Conway's method great power to reveal hidden relations among tangles.

For example, note that if you start with any number and take its negative reciprocal twice, you get back the same number. Translated into the language of tangles, that fact implies that rotating any tangle twice must give the same tangle back again. But if you try rotating the –3/5 tangle twice (or, equivalently, turn the diagram upside down), the resultant tangle will not look at all the same. Nevertheless, it is possible to manipulate the strings in the upside-down version to get the right-side-up version. And even more-subtle relations among tangles can readily be proved. For example, given any rational tangle, the sequence of moves *twist-turn-twist-turn-twist-turn* will produce an equivalent tangle. Can you see why?

GIVEN MATHEMATICIANS' PASSION FOR GENERALIZING, it should come as no surprise that *twist, turn* and their arithmetic analogues have applications extending far beyond rational tangles. Nowadays mathematicians tend to take those benefits of noncommutativity for granted. It is hard to believe that, a little more than a century and a half ago, the best mathematical minds in the world would have found them inconceivable.

The man who unleashed noncommutativity was William Rowan Hamilton, an Irish mathematical prodigy who was appointed Royal Astronomer of Ireland at the age of twenty-two and was knighted at thirty. Hamilton had reached the advanced age of thirty-eight when, on October 16, 1843, he had a flash of inspiration that helped him solve a problem that had vexed him for more than ten years. Hamilton was one of the first scientists to appreciate the importance of complex numbers—numbers that incorporate multiples of the square root of –1. Such peculiar numbers crop up naturally as solutions to many algebraic equations. The Greek mathematician Heron had considered them as early as 100

A.D., but only in the early 1800s did they become a fully accepted part of the mathematical repertoire.

Hamilton had been working intensely to discover new number systems "beyond" the complex numbers. Because ordinary real and complex numbers obey the rules of arithmetic—rules such as associativity and commutativity of addition and multiplication—Hamilton expected to discover more exotic numbers that do the same. But try as he might, he could not find them. (Mathematicians now know that no such numbers exist.) Finally Hamilton realized he could settle for second best. On that autumn day he envisioned a number system satisfying all the usual rules but one: the commutative law of multiplication. He called his new system the quaternions.

*Rimma Gerlovina and Valeriy Gerlovin,* Absolute-Relative, *1990*

By the end of the nineteenth century, quaternions had been largely superseded by more versatile tools. But their discovery left at least one enduring legacy: it freed mathematicians to make up new algebraic structures that flouted some of the rules of conventional arithmetic. Such structures—which go by names such as groups, rings and Clifford algebras (the latter being the most successful modern generalization of quaternions)—are now part of the stock-in-trade of the research mathematician.

HAMILTON'S SPIRIT LIVES ON IN THE WORK OF contemporary noncommutative geometers. By taking a kind of algebraic structure discovered in the 1940s and crossing commutativity off its list of axioms, they have made it possible to envision new kinds of geometric space. Their work has also been profoundly influenced by another noncommutative surprise from the realm of physics.

In the early years of the twentieth century, the physics of the subatomic world seemed to grow progressively stranger. Until 1925, when Heisenberg sketched out the mathematical formalism of modern quantum physics, particles such as photons or electrons were considered to be pointlike objects that could be tagged with numbers representing observable quantities, such as energy. In the new theory, physicists stepped through the looking glass. Observable quantities such as energy were no longer numbers but so-called operators, or actions, performed on a particle. Particles themselves were not points but wave functions: formulas that, roughly speaking, express the probability that a particle will be observed at any particular location. A particle might be either pointlike or wavelike, depending on the form of its wave function. A pointlike particle has an extremely concentrated wave function; a wavelike particle has one that is more spread out.

As I mentioned earlier, real numbers commute, but actions generally do not (remember my misadventure with the cocoa). By reinterpreting observables as operators, Heisenberg inevitably introduced the idea of noncommutativity. In particular, he discovered that the actions "measure the position of" and "measure the momentum of" do not commute. When you measure the position of a particle, you alter its state in such a way that its original momentum cannot be known with complete accuracy. Thus Heisenberg's uncertainty principle, the statement that a particle's position and momentum cannot be known simultaneously, is a consequence of noncommutativity.

In recent years mathematicians and physicists have taken noncommutativity to extremes that Heisenberg and his colleagues never dreamed of. The founders of quantum theory may have been radicals when dealing with matter and energy, but they were laissez-faire conservatives when it came to the geometry of space. They assumed the universe is what mathematicians call a manifold, which is something like a smooth, unbroken rubber sheet with no edges or creases [see Daniel Asimov, "There's No Space Like Home," *The Sciences,* September/October 1995]. In one respect, manifolds are paragons of commutativity. It does not matter whether you measure the position of a particle first along a horizontal axis and then along a vertical one, or vice versa; you get the same result either way.

About fifteen years ago, however, theoreticians began devising bizarre new spaces—nonclassical spaces in which even such basic operations as "measure the distance from the back wall" and "measure the distance from the side wall"

fail to commute. Because noncommutativity translates into uncertainty, those distances cannot be known simultaneously. Imagine trying to find your shoes in such a quantum closet: as soon as you figured out exactly where they were from left to right, they would turn into a front-to-back blur.

Noncommutative spaces have opened new vistas in geometry the way quantum theory did in physics. Ever since Euclid, geometers have regarded points as fundamental: the "atoms" from which all other geometric structures are built, the fuel for functions, mathematical relations that turn points into numbers. Noncommutative geometers seize that 2,000-year-old tradition and throw it out the window. Following Heisenberg, they recast geometry so that the fundamental concept is no longer *point* but *function*—just as quantum physicists replaced the idea of *particle* with that of *wave function*.

The picture that emerges is a shadowy dreamworld, a world made up entirely of verbs and devoid of nouns, a world in which the only realities are actions and in which no objects (points, particles) exist for the actions to act on. Mathematicians may be quite happy living in such a shadow land, but to understand what it means for the observable world, they have to figure out how to get back. They must reverse-engineer the functions into points, until every object or relation in one space has an interpretation in the other. Making such a correspondence is much like what Conway did in finding a numerical way to talk about tangles of string. Once he had found the correspondence, he could manipulate numbers arithmetically much more easily than he could manipulate knots of string, thereby discovering hidden relations among various kinds of knots.

THE PICTURE THAT EMERGES *from noncommutative geometry is a shadowy dreamworld made up of verbs and devoid of nouns.*

THE RESOLUTION TO THE REVERSE-ENGINEERING problem came in 1943, in a theorem proved by the former Soviet mathematician Israel M. Gelfand, now at Rutgers University in New Brunswick, New Jersey. Gelfand's method of reconstructing space was both elegant and ironic. In a world where verbs are the objects, he pointed out, the nouns become actions. In a sense, Gelfand gave a mathematical answer to the question with which the Irish poet William Butler Yeats ended his poem "Among School Children": "How can we know the dancer from the dance?" The dancers are points; the dances, functions. In Gelfand's approach (contrary to the usual way of thinking about such things) the dance comes first and summons the dancer into existence. To discover a dancer's identity—to "know the dancer," in Yeats's words—one need only watch the dancer perform: not just one dance, though, but every possible dance.

According to Gelfand's theorem, the idea of reconstructing space will work provided the shadow land of functions (which mathematicians call by the uninformative name of "commutative C-star algebras") obeys a short list of specifications, or axioms. Foremost on the list is commutativity: the multiplication of functions is just as commutative as the multiplication of real numbers. But suppose that, in the spirit of William Rowan Hamilton, you take that list of axioms and cross commutativity off it. With that restriction lifted, hitherto forbidden noncommutative functions come swarming out of the axiomatic system like the contents of Pandora's box. What kind of space will result?

The simplest example of such a space comes from Alain Connes, a mathematics professor at the Collège de France in Bures-sur-Yvette, France. Connes (the name rhymes with *gun*) is generally considered the founder of noncommutative geometry; his work has won him the Fields Medal, the mathematical equivalent of a Nobel prize. His space is made up of only two points. An ordinary function on such a space could simply be represented as a pair of numbers. But Connes does something extraordinary. Writing those two numbers in the corners of a two-by-two array, he turns the ordinary functions into the tame inhabitants of a well-known noncommutative algebra, the two-by-two matrices. Among those matrices is one that has the vexing power to change either point into the other one. That matrix is a legitimate citizen of the space, and there is no way to insulate the points from its effects. As a result, it is impossible to tell the two points apart. Now *that* is an uncertainty principle!

THE EXAMPLE MAY BE PLAYFUL, BUT IT IS FAR from frivolous. Connes has shown that a slight elaboration of the two-point space yields a model of the universe that makes the same predictions as the physical theory that unifies the electromagnetic force with the weak force responsible for radioactive decay. With further modifications, Connes says, he can incorporate the third fundamental force of physics, the strong nuclear force, as well.

The essence of quantum space, you will recall, is that it is permeated with uncertainty. The space of Connes's model has a much more conventional flavor. In it, as in his two-point space, every point is twinned with an indistinguishable alter ego. Within the space itself, classical certainty prevails; the only uncertainty comes from not knowing which point you are dealing with (which quantum closet your shoes are in, so to speak). But that uncertainty, Connes says, is enough to generate the entire standard model of elementary particle interactions.

But Connes's model can make predictions that the standard model cannot match. For example, in 1995, the physicists Bruno Iochum, Daniel Kastler and Thomas Schücker of the Centre de Physique Théorique in Marseille, France, showed that, if Connes's framework is correct, the mass of a theoretically postulated particle called the Higgs boson can be computed precisely, once the mass of the so-called top quark is determined. No one yet has observed a Higgs boson, but Iochum and his colleagues are confident they have discovered a link between the Higgs and the top quark. "We believe that noncommutative geometry is about to revolutionize physics to the same extent as . . . Riemannian geometry did," their paper proclaimed.

But Connes himself stresses that noncommutative geometry is more than just a tool for studying quantum field theory. Even if it fails to fulfill the dreams of physicists, it will remain valid, and valuable, mathematics. And other recent additions to the bestiary of nonclassical spaces could become better understood in the context of Connes's new formulation. Fractals—those infinitely filigreed, infinitely self-referential figures that have become a staple of pop art and pop science—find a natural home in noncommutative geometry. So do nonperiodic tilings: patterns formed by shapes that fit together, snugly and endlessly, without ever repeating themselves. To mathematicians, the most breathtaking thing about Connes's work may be the ease with which it fits such apparently unrelated concepts into a single framework.

In noncommutative geometry there is a technical operation for merging certain objects. Mathematicians jokingly call it "Connes fusion." The pun could be emblematic of the field as a whole: a new paradigm that fuses many specific examples too unruly to fit into the classical theories of space. Now that the hidden link of noncommutativity has come out into the open, mathematicians can expect to learn more by looking for it than they did when they merely let it take them by surprise. ●

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*Yayoi Kusama,* Repetitive Vision, *1996*

*Nancy Chunn,* December 1, 1995, *1995*

# The Power of HIV-Positive Thinking

*When desperate men insisted that good testing procedures were killing them, they changed the practice of medical research. Can science afford to be this democratic?*

BY STANLEY J. HEGINBOTHAM

Impure Science: AIDS, Activism, and the Politics of Knowledge
*by Steven Epstein*
*University of California Press, 1996*
*466 pages; $29.95*

**Item:** In 1985 a steady stream of independent couriers began running shipments of antiviral drugs into the United States. The drugs, which had not been approved for use in the U.S., initially came from Mexican *farmacias,* but sources soon diversified, and the disparate efforts merged into a loose-knit smuggling organization. "Buyers clubs" and "guerrilla clinics" were formed in major cities around the country, as well as in Canada and England, selling a range of unapproved drugs and "alternative" therapies.

**Item:** In 1988 attendees at the annual meeting of the Infectious Diseases Society of America received dire warnings about the integrity of certain controlled disease studies. Research study centers reported a nationwide pattern that was contaminating study designs: Subjects were taking the study treatments along with alternative treatments. Patients were resorting to cheating, even bribery, to gain entry to trials and, once in a trial, they were mixing and sharing drugs to dilute the risk of being on a placebo. Many people who concluded they were on a placebo were dropping out of the trials.

**Item:** Later the same year, in response to charges that certain unapproved drugs were available to some patient populations but denied to others, the commissioner of the U.S. Food and Drug Administration (FDA) announced that the agency would permit limited imports of the drugs. Another federal official suggested the decision showed that the commissioner had gone temporarily insane.

**Item:** At about the same time, an organization in New York City began conducting clinical trials in which patients helped decide which trials the organization should conduct and how to set them up. Patients also helped set policies on the use of placebos and on the demography of patients who could participate.

**Item:** In 1990 the head of an institute of the National Institutes of Health (NIH) gave members of a group of activist patients regular seats at meetings of a major NIH clinical trials group, which had previously opened its doors only to scientific investigators and representatives of research sites. The institute head reportedly forced the group of principal investigators to agree that subsequent meetings, including those of its executive committee, should be open to such lay outsiders.

Research science jealously guards its autonomy. Like other professions, it has developed elaborate training mechanisms, sophisticated vocabularies, intricate prestige hierarchies and specialized procedures for validating and communicating its work. Those practices serve a number of useful scientific ends. But they also serve to insulate and protect scientists from outsiders who want to influence scientific work.

Medical research science has to work particularly hard to shield its autonomy and integrity from outside forces. The reason is clear: the work of medical science eventually touches the health and well-being of everyone. Because of the continuing public fascination with medical science (in contrast with, say, the fickle public interest in superconductivity), medical research scientists have built barriers between themselves and the patient community that are normally buttressed by a formidable complex of intermediary institutions. Among them are practicing physicians, whose profession has elaborate protective mechanisms of its own; government agencies that fund and judge the safety and efficacy of the products made by research science; and pharmaceutical companies, which develop and market those products.

Those middlemen have developed enough expertise in the mores and needs of research science that they have gained a certain measure of access to the medical research community. Naturally, they protect that access for themselves, making it all the more difficult for the lowly patient to penetrate the defenses of pure science.

Yet each of the vignettes reported above, distilled from Steven Epstein's important and compelling new book, *Impure Science,* shows how medical consumers have been able to cross the barriers of medical science and infiltrate its most restricted domains. Taken together, the vignettes pose, in the eyes of some, an alarming threat to the integrity of the scientific method itself. Indeed, Epstein's larger story tells how nonscientists not only passed into the inner sanctums of scientific research but forced change in the very procedures scientists rely on to measure and interpret their work. The story can be read as one in which scientific purity was repeatedly and systematically compromised by the intrusions of political activists who lacked scientific credentials and who challenged scientific norms out of self-interest.

Still, some of the scientists who bore the brunt of the assault seem genuinely to have changed their view of what good science demands of them. Read with an open mind, then, Epstein's book raises challenging questions about how relations between medical science and patient communities should be managed.

MOST PATIENTS DEAL DIRECTLY with and defer to their physicians. They have limited knowledge of or contact with other patients afflicted with the same disease. When physicians think a patient could benefit from an unproven treatment, they may enroll the patient in a test of the safety and efficacy of the treatment. The understanding from the outset is that neither the patient-subject nor the physician will know whether the patient will receive the treatment or a harmless placebo. Such a "double-blind" placebo design has long been considered essential for maintaining the integrity of a scientific test.

Some patients want to learn as much as possible about their condition and the treatment alternatives. Typically, though, such patients face formidable challenges: finding and grasping the relevant literature, identifying and talking with other people who have the same disease, and coping with the disease itself. Often that self-management is cut short because the disease resolves itself quickly in death, disability or recovery. All those realities limit the duration and intensity of patients' efforts to learn about their disease.

Even when patients have a relatively sophisticated understanding of their condition, they are not likely to enlist that understanding for more than making intelligent choices from the alternatives posed or accepted by their physicians. To challenge a physician's expertise, let alone the scientific research and procedures that inform it, usually seems like a lonely and hopeless task.

Several groups of patients have nonetheless sought out others with the same disease, joined together and had substantial success in shaping the practice of scientific medicine: one thinks particularly of women who successfully demanded a wider range of options for treating breast cancer and pushed for research on such treatments [see "Our Bodies, Our Science," by Charles Weijer, *The Sciences,* May/June 1995]. What makes *Impure Science* such a rewarding read is that it zeros in on a social, scientific and medical phenomenon that seems almost to have been designed to penetrate the walls of medical scientific research.

*Robert Morris,* Private Silence/Public Violence, *1989*

IN THE EARLY 1980S GAY MEN IN SAN FRANCISCO and New York became aware of a syndrome, contracted by sexually active and promiscuous gay men, that led to death from rare forms of cancer and pneumonia. Gays in both cities already had well-developed inter-

personal networks, as well as special-interest newspapers and magazines, which quickly alerted them to the new danger. Evidence soon indicated that the syndrome, once established, was likely to kill. By 1985, patients who were told of the mere presence of antibodies for a particular retrovirus in their blood interpreted the news as a death sentence: after an indeterminate symptom-free period, they faced agonizing illnesses and eventual demise.

But gays had long been told by much of the medical community that their sexual preference was a form of illness. Little wonder, then, that many of them disparaged the authority of medicine, particularly when it came to issues related to gay sexuality. Unprepared to accept medical wisdom at face value, they began in earnest to study the science and medicine underlying their own conditions. Few were themselves scientists, but many were intellectuals who, given the depth of their concerns, were not easily intimidated by the assumed knowledge, specialized vocabulary, testing procedures and logic of the emerging scientific literature on what quickly became known as HIV and AIDS. One early gay activist recalled the time:

*Hannah Wilke,* Why Not Sneeze? *1992*

When we first started out, there were maybe three physicians in the metropolitan New York area who would even give us a simple nod of the head. Now, every day, the phone rings ten times, and there's a physician on the other end wanting advice. [From] me! I'm trained as an opera singer!

Thus a highly motivated, well-educated and organized gay community began a frontal assault on the barriers that were protecting the autonomy and integrity—the purity—of scientific research and clinical practice on AIDS and HIV. Epstein tells the stories of the intellectual, moral and political battles that ensued. As the vignettes at the beginning of this essay suggest, gay activists often succeeded in breaching the barriers and modifying the practices of physicians, pharmaceutical companies, federal funders, federal regulatory agencies and the research scientists themselves.

In the first part of his book Epstein provides a little-known but revealing perspective on the widely reported conflicts about what causes AIDS. He describes how Robert C. Gallo, then of the National Cancer Institute, fought with Luc Montagnier of the Pasteur Institute in Paris over which group had discovered the retrovirus that, both were persuaded, caused the failings of the immune system that, in turn, resulted in AIDS. Gallo, in pressing his claim for priority, also argued that evidence implicating the retrovirus was so persuasive that research directed toward a cure and a vaccine for the disease should abandon all other theories about causation and focus solely on the retrovirus. The retrovirus has come to be known as HIV.

Gallo's stand on causation pitted his laboratory, as well as a rapidly evolving consensus within the research community, against Peter Duesberg, a widely respected virologist at the University of California, Berkeley. Duesberg's research suggested to him that the great majority of retroviruses are benign. Moreover, given the available data, he could see no plausible way to explain how HIV could cause AIDS-related diseases. Instead, he argued, HIV is simply an opportunistic infection that appears frequently in conjunction with diseases that are linked to AIDS but have other causes.

Duesberg reinforced his skepticism with a long-standing methodological point. Bacteriologists are warned not to accept a bacterial or viral agent as a cause of a disease until they have satisfied four criteria, first set forth by the nineteenth-century German microbiologist Robert Koch: First, the agent should be found in all cases of the disease. Second, workers should be able to isolate and grow it in a pure culture that, third, gives rise to the disease when injected into a susceptible laboratory animal, from which, fourth, the agent is then recovered.

By the Koch postulates Gallo lacked the grounds for declaring HIV causes AIDS. Most people who tested positive for HIV antibodies showed no sign of AIDS. Moreover, investigators had not been able to produce the disease in experimental animals. But epidemiological data linked HIV to AIDS, and other retroviruses Gallo had studied exhibited a pathogenetic character. Gallo wrote that the evidence for the causal role of HIV was "overwhelming."

Epstein describes how such a seemingly arcane dispute over the adequacy of scientific evidence became politicized

by gay activists, then transformed and given new life. Soon after the discovery of the "syndrome," physicians and journalists had polarized into two camps over the central issue of cause. Were excessive drug use and promiscuity simply overloading the immune system, as one camp maintained, creating a susceptibility to rare forms of cancer and pneumonia? Or, as the second camp had it, was some other causal agent at work? Gallo's claim to have identified HIV as the cause supported the second camp, and further investigations soon led to hopeful evidence that a drug called AZT might inhibit the spread of HIV. Duesberg's challenge, however, gave ammunition to the first camp, lending plausibility to their argument that AZT is a "poisonous" drug that would do nothing to change the basic lifestyle that, they asserted, causes AIDS.

In 1987 John Lauritsen, a partisan of the lifestyle view of causation, published an influential article about Duesberg in a gay publication, the *New York Native*. Lauritsen concluded his article with a flourish: "Unless HIV's champions can do some very fancy explaining, . . . Duesberg's article has unambiguously relegated the 'AIDS virus' etiology to medical history's trash heap." But for Duesberg's methodological challenge to support that conclusion and derail the scientific establishment's commitment to the causal role of HIV, it seemed critical to present a plausible alternative explanation. In a follow-up interview for the *Native,* Lauritsen, Epstein argues, led a reluctant Duesberg to commit to such an alternative:

He described for Duesberg what he called the "profile" of the average AIDS patient—a profile whose characteristics supposedly included long-term drug abuse, promiscuity, and repeated cases of sexually transmitted disease:

[Lauritsen:] Looking at that profile . . . I think it would be surprising if such people did not become seriously sick from their lifestyle.

[Duesberg:] I would be surprised, too. The number of contacts, the number of things they inject. You wonder how they could do it.

Whereas Duesberg had at first found it hard to argue his case persuasively in the scientific community, the case made on his behalf by Lauritsen quickly became grist for the mainstream media (aided in no small part by a vigorous promotional campaign by the publisher of the *Native*). Duesberg's argument quickly became a major public-relations challenge for Gallo, for the HIV-focused research community and for those who thought that AZT was helpful in treating AIDS. It was the lay press, building on a case developed in the gay press, that effectively forced scientific journals and then the research community to reexamine the issue of what causes AIDS. That reexamination, one can now say with hindsight, yielded increasingly conclusive evidence that HIV is the culprit. Yet once the uncertain evidentiary basis of the early authoritative declarations of HIV's guilt was exposed, it was remarkably difficult for science, even possessed of that new evidence, to "prove" that guilt to the full satisfaction of the public.

Although Epstein devotes almost half his book to the politics of establishing the cause of AIDS, the stories in the second half, about the politics of its treatment, are even more compelling and instructive.

Once the U.S. and French research and pharmaceutical communities focused attention on HIV as the presumptive cause of AIDS, they quickly identified several drugs known to inhibit in animals the enzyme, called reverse transcriptase, that enabled many previously studied retroviruses to take over the genetic machinery of their hosts. AIDS patients, faced with physical deterioration, excruciating suffering and near-certain death, were promptly alerted by the gay media and informal networks to new drugs or treatments that might slow the spread of their disease.

**Gallo's stand that HIV causes AIDS pitted him against Duesberg.**
***For Duesberg's supporters, the anti-HIV drug AZT was merely "poisonous."***

In their desperation to try any plausible remedy, they quickly discovered ribavirin. One of the possible reverse-transcriptase inhibitors, the drug was only in early clinical trials in the U.S., but it was legally available at low cost in Mexico. Furthermore, the patient community found that another antiviral drug, HPA-23, not yet in trials in the U.S., was legally available in France. The scientists' misgivings about both the effectiveness and safety of those drugs seemed perversely misguided to patients who were facing imminent death. The FDA quickly authorized "compassionate use" of several reverse-transcriptase inhibitors—even though they were soon found to be neither effective nor safe.

Within months the politics of the FDA approval of drugs was greatly complicated by preliminary evidence from Phase I trials of AZT. Those trials found that the drug not only met the safety standards required to justify further testing, but that it also seemed to slow HIV replication, boost immune systems and relieve some AIDS symptoms. The tremendous demand for immediate access to AZT put the FDA under intense pressure to release the drug for general use—*before* trials could reliably determine who should be taking it and in what amounts. As additional drugs became available for testing, attacks on the FDA for withholding them pending orderly testing became vicious. Finally, in July 1988, the FDA commissioner announced that the agency would permit unapproved AIDS drugs to be imported in small quantities for personal use.

Many in the research community, as the journal *Science* reported at the time, were "stunned" by the shift in FDA policy. At issue was not simply whether untested drugs were safe and effective. More serious to medical investigators was the problem of managing the usual double-blind placebo

tests when the drugs were readily available outside the controlled context of the clinical trials.

Epstein is at his best in describing the emotion and logic of scientists, physicians, federal bureaucrats and patients affected by the issue. Investigators had already seen, in the AZT approval process two years earlier, what happens when AIDS patients legitimately believe that being assigned to the placebo arm of clinical drug trials is tantamount to a death warrant. Many had simply refused to take the risk, when they could get AZT outside the trials. Others who joined the trials had shared their medicines in an effort to ensure that everyone got at least some AZT, thereby subverting the trial design. The leadership of the institutes of NIH had to face what activists asserted were the genocidal consequences of the procedural norms.

The fact that creative compromises were hammered out to meet the pragmatic, if not the ideal, needs of science, while providing reasonable patient access to unproven drugs, is a tribute to leaders on both sides of the controversy. The ability of a remarkably powerful activist movement to force its concerns on the scientific community revealed, in the process, the sometimes rigid and heartless results of research and clinical protocols. At the same time, the disruptive consequences of activism reminded scientists and clinicians of the benefits of being able to pursue their work relatively free from political pressures.

Epstein uses his detailed knowledge of the rival perspectives and strategies within the U.S. gay community to excellent effect, and that focus gives the book impressive conceptual coherence and clarity. But the activist-induced politics of AIDS stretches far beyond the American gay community. Other groups in the U.S. affected by AIDS enter his narrative primarily as they impinge on the efforts of gay activists. The concerns and internal politics of African-American and hemophilia activists are not handled with anything like the nuance and sensitivity that characterize Epstein's treatment of gay activists. And issues that have been important in the politics of AIDS—such as to what extent education should focus on the dangers of sexual transmission to and among heterosexuals—go untreated. Read as a study of gay activism and AIDS in the U.S., the book is excellent. One needs to look elsewhere, however, for treatment of other aspects of the domestic—and all aspects of the international—politics of AIDS.

The internal politics of the scientific communities is also largely missing from *Impure Science*. The story focuses on the targets of gay activism, primarily in the FDA and NIH. Epstein seems fair and balanced in his treatment of the scientists and bureaucrats whose encounters with gay activists he describes. But he is only peripherally interested in the bureaucratic and laboratory politics that surrounded them. That, too, is a story waiting to be told.

No one who values science wants a repetition of the attacks on it that Epstein recounts. Those attacks disrupted valuable research procedures and protocols and, in the process, almost certainly slowed down scientific advances in the understanding and treatment of AIDS. But how can science better respond to future challenges from new communities of patients? Some will argue that the answer lies in bigger and better defenses. Epstein's account, however, is a reminder that the insulation of medical scientists from communities of patients can foster insensitivity to the very patients the scientists are trying to help.

The more appropriate conclusion is that medical science needs to listen to and blend the perspectives of patient communities in its advisory and review procedures. Some programs are already experimenting with such approaches. Making those efforts productive and rewarding will be a difficult job—but not nearly as costly or as detrimental as ignoring the disaffected patient communities of the future. ●

***Stanley J. Heginbotham*** *is a visiting scholar at the New York Academy of Sciences. He is at work on a book on the challenges of identifying scientific merit in the peer-review process.*

*Keith Haring,* Ignorance=Fear/Silence=Death, *1989*

# Books in Brief

LAURENCE A. MARSCHALL

## Shelf Life

*Cold-war submarines find new applications in the hands of oceanographers*

*Deborah Brown,* Olympic, *1990*

THE UNIVERSE BELOW
*by William J. Broad*
*Simon & Schuster, 1997*
*432 pages; $30.00*

DURING THE MID-1960S, AS NASA press releases trumpeted the latest progress in the race to the moon, the U.S. Navy was secretly mounting an expedition to an equally mysterious and hostile environment: the depths of the ocean. Both ventures were sparked by the cold war. But whereas the space race sprang from a can-do sense of national pride, deep-sea exploration was motivated primarily by the perverse imperatives of national security. The Soviets, it seemed, had the habit of lofting test missiles into the north Pacific, where dummy nuclear warheads could be hidden from prying eyes a couple of miles down. Occasionally the Soviets also lost a submarine or a plane, loaded with codes and electronic equipment—the kind of stuff intelligence officers would kill to see. And because the Americans occasionally lost subs or planes too, they also wanted to get their stuff back before the enemy could salvage it.

The demand for deep-sea survey and retrieval devices was so pressing that it called for an effort of Apollonian proportions, even though the task was perhaps more difficult than putting a man on the moon. In space, at least, the target was always in sight. But the ocean depths were perpetually dark; even with searchlights it was hard to see more than a few dozen feet.

Today, with a quarter century of hindsight, the race to the ocean bottom seems a triumph of high technology and heavy industry. By the end of the 1960s a flotilla of small manned and robotic exploring craft, equipped with sonar, video cameras and arms for picking up objects, could be called into position for a wide variety of underwater tasks. A seven-person nuclear-powered submarine, the NR-1, was designed to dive a few thousand feet down and could stay submerged for weeks at a time. It even had wheels for rolling over the ocean floor. Another sub, the *Halibut,* was outfitted as an undersea barge for salvaging materials right under the Soviets' noses. While submerged, the mammoth craft could winch out cables from an internal bay, lower reconnaissance devices into the abyss and haul up the hardware it found, all without a ripple on the ocean surface.

As the cold war wound down, the benthic armada it had spawned went public. The result, according to the science reporter William J. Broad of *The New York Times,* is an "opening up" of the oceans that is as historically significant as the California gold rush. The technological bonanza has revealed a rich ecosystem of exotic tube worms and primitive bacteria, thriving without sunlight on the energy of volcanic vents. But the undersea technology has also exposed the ocean floor to the threat of commercialism—most trenchantly with the public salvage of the *Titanic.*

Because so much of the earth's surface and most of the vast volume of the biosphere lie within the ocean basins, the importance to science of this oceanic revolution cannot be overestimated. Broad tells absorbing stories of the investigators who unravel secrets of the deep ocean, and of the entrepreneurs who seek to extract its animal and mineral riches. Yet his book can only skim the surface of an environment where, in an ecological echo of cold war geopolitics, many of the battles of the next century will be fought. In a realm that is only beginning to reveal the nature of its ecology, the line between exploitation and sustainable development is exceedingly narrow.

## In the Company of Mushrooms

*by Elio Schaechter*
*Harvard University Press, 1997*
*280 pages; $24.95*

"Crimini!" I exclaimed, halfway through this charming story of one man's love affair with mushrooms. "Fungi aren't quite as yucky as I thought." My mistaken assumption (which you may well share) had been that, because mushrooms thrive in dankness and decay, they are themselves decaying matter. Far from it, writes Elio Schaechter, an emeritus professor of microbiology at Tufts University School of Medicine in Boston, Massachusetts. Mushrooms are part of the regenerative process—the stuff of birth, not death. They are the fruiting appendages of one or another kind of fungus, whose body—a large mat of thin filaments called the mycelium—is seldom noticed by the casual observer amid the dirt, roots or other organic material that surround it. A mycelium produces mushrooms for only a short period, when conditions are ideal for reproduction. That is why, after a sudden spring rain, delicate white caps literally "mushroom" into existence on a well-mowed lawn.

Judge them neither by their surroundings nor their appearance, cautions the author, for a mushroom's bizarre shape, unappetizing odor or slimy texture can conceal a morsel of incomparable gustatory value. The waxy cap, *Hygrophorus fuligneus,* is delicious sautéed with onions, celery, parsley, cream, chives and a dash of wine. But first a "thick, translucent, glutinous layer" of sticky secretion must be removed, along with any dirt and pine needles that stuck on while the mushroom was collected. *Laetiporus sulphureus,* a woody bracket fungus that attaches like a shelf to dead trees, is considered a delicacy by many collectors. Because of its poultry-like taste and consistency, it is commonly called the chicken mushroom. Even the stinkhorn, *Phallus impudicus,* which resembles a human penis and has an unforgettable aroma of rotting flesh, makes "a flavorful dish," Schaechter writes, "with a subtle, radish-like flavor."

On one matter, however, I seem to be right: mushrooms can be dangerous. There are mushrooms that can upset your stomach, others that induce hallucinations and others that kill. Some mushroomers, no doubt, like to flirt with death, the way some sushi lovers eat the poisonous blowfish, fugu. But Schaechter is not among them. He eats only what he has learned to identify through many years of apprenticeship, and he will, at most, nibble small portions of a suspicious specimen. A conservative approach to mycophagy, Schaechter assures us, can prevent an early demise and guarantee many tasty meals.

The best way to achieve that happy state of affairs, the author believes, is to learn as he learned, strolling in the woods with a group of like-minded mushroom lovers. Accordingly, along with a wealth of lore about the natural history of fungi and the social history of the people who hunt them, Schaechter provides a lengthy list of clubs in the United States and Canada where amateurs can learn mycogastronomy firsthand. In short, here's a book where you're sure to find a good story with an uplifting morel.

## Stuff

*by Ivan Amato*
*BasicBooks, 1997*
*294 pages; $25.00*

The world, according to the science writer Ivan Amato, is made not of rock, water and air, but of Portland cement, stainless steel, polymethyl methacrylate, spandex and boron-doped silicon. That should come as no surprise, even to the natural-foods-and-fibers fanatics among us. Civilizations have long been characterized by the materials they use, and people have created new substances from old ever since the first Stone Age hunter discovered how to turn a lion's hide into a loincloth. Survival and success, then as now, depended on the ability to use the right material to make the right tool for the task at hand.

But fashioning the right stuff is tricky business. For most of history people have come up with new materials by chance, not by contrivance. The Roman historian Pliny the Elder tells of Phoenician sailors, cooking on a sandy beach, who propped up a clay pot on a block of charred wood. Heat and organic ash, they noticed, turned the sand below into a translucent material that was moldable and malleable when hot, and watertight when cool. Let us clink our glasses to their good fortune!

In the nineteenth century the hardware merchant Charles Goodyear tried mixing natural rubber with substance after substance to make the rubber more flexible and durable. Then he accidentally spilled raw latex and a bit of sulfur onto a hot stove, and voilà! the recipe for vulcanization. Thomas Edison preached about the benefits of systematic research when the quarry was, say, the best material from which to make filaments for incandescent lamps. But his remark that genius is 99 percent perspiration and 1 percent inspiration suggests he employed trial and error much more frequently than directed design.

In the past fifty years, insights from chemistry, quantum physics, mineralogy and engineering have coalesced into a new discipline. Known as materials science and engineering, it aims at taking the element of chance out of the search for the right stuff. The success of materials science has been driven by the multidisciplinary needs of defense and industry, accelerated by massive coordinated efforts such as the Manhattan project and the Apollo program. Need a lightweight, high-strength coating for a jet fighter? A polymer that can protect a Green Beret from automatic-weapons fire? A superstrong magnet to make small and efficient refrigerator motors? Materials scientists can often figure out just how atoms and molecules should be arranged to meet your needs—and then mix up as much material as you want at a price you can afford.

The success of such a bold endeavor depends on a host of developments in physics and chemistry. New analytic tools, such as the scanning probe microscope, have enabled investigators to tease apart the microscopic structures of materials, thereby explaining how the gross properties of a substance depend on the arrangement of its constituent atoms and molecules. New fabrication techniques synthesize naturally occurring microstructures as well as novel ones. Molecular-beam epitaxy, for instance, lays down microscopic layers of atoms in crystals with such precision that no more than three atoms are out of place on a chip one centimeter square. And new theoretical techniques, exploiting powerful computer models, help investigators envision materials with unprecedented properties—compounds harder than diamond, for instance [see "Harder than Diamonds?", by Marvin L. Cohen, *The Sciences,* May/June 1994].

Of course, materials scientists can't yet cook up anything they imagine. They still can't make a 300-horsepower V-8 engine block light enough to lift with your pinky, or a laptop that runs for a year on a pair of triple-A batteries. But Amato, who covered materials at *Science News* for four years, shows how far they have come from the hit-and-miss alchemy of the past, and how much promise there is in the material world of the future. ●

***Laurence A. Marschall,*** *author of* The Supernova Story, *is a professor of physics at Gettysburg College in Pennsylvania.*

*Continued from Page 11*

don't try to measure the spin or otherwise disturb it, the qubit can remain in a superposed (or ambiguous) state, and as such, it stores both a 1 and a 0 simultaneously. It is that superposed state that gives rise to the enormous potential power of quantum computing.

The key to that power is that qubits can become "entangled." In ordinary computing, if you copy the value of one bit to a second bit, the second bit becomes a 1 if the first bit is a 1 (and a 0 if the first bit is a 0). In the analogous operation on qubits, if you "copy" the value of a nuclear spin of one nucleus in a superposed state to a second nucleus, both nuclei go into a second superposed state that is "entangled" in a sense pointed out many years ago by Einstein. The entangled state is such that if you measure the spin of either one of the nuclei, the spin of the other nucleus will instantaneously take on the same value you measured for the first. The quantum operation of "copy," known as a controlled-NOT, has effectively operated on all possible ordinary input states at once—in this case both the 1 and 0 that are the possible input states of the first bit.

A controlled-NOT is only one of several operations you can perform on qubits, taking them from one superposed state to another. If, for instance, you were to apply the quantum-entanglement operation NOT to some number of qubits *N,* the operation would simultaneously flip the 1 and 0 values of all possible strings of *N* bits, effectively operating on $2^N$ input strings at once. Only at the end of a sequence of such operations, when you "read" the results of such a computation, do you measure the spins of any of the nuclei. At that moment, and not before, you "collapse" the superposed states into definite values of spin. In a sense, then, computation with superposed states is computation on all possible inputs at once. Shor's algorithm for factoring large numbers is the first to exploit those properties of quantum systems for problems of practical importance.

THOSE PRINCIPLES HAVE BEEN KNOWN since the early 1980s, but some fine print in the laws of quantum mechanics made them extremely hard to exploit. In order for an atom to remain in both states at once (or to be "coherent" in quantum-mechanical terms) it needs absolute isolation. If anything disturbs it—a vibration, a passing photon, a blaring boom box—it decoheres, becoming a 1 or a 0 rather than both at the same time. In order for a computer to compute, however, its bits must be prepared, manipulated and measured. How can a quantum computer processor hope to switch from one superposed quantum state to another without a little prodding?

In previous experiments investigators

attempted quantum computing with a single atom, but the atom is devilishly difficult to isolate from its environment. Gershenfeld and Chuang tried a much simpler approach. Rather than using entire atoms as qubits, they used atomic nuclei in molecules of ordinary substances, such as the caffeine in coffee. Because such nuclei are naturally isolated from the environment, they can maintain their coherence for as long as several thousand seconds.

After placing their sample in a magnetic field, the investigators delicately probed it with high-frequency radio pulses, which revealed the net direction of the sample's nuclear spins. Depending on how the pulse-generating machine is programmed, its pulses execute various algorithms to which the final state of the sample is a solution. Gershenfeld and Chuang were not the first to think of using such nuclear magnetic resonance (NMR) techniques for quantum computation. But previous investigators assumed that the random spin directions within a bulk sample would cancel out any computation. For the technique to work, they thought, all of the nuclei would have to exhibit the same spin.

GERSHENFELD AND CHUANG WERE willing to be slightly less purist. They realized they could compute simultaneously with a vast number (though not all) of the molecules in a bulk sample at room temperature by treating each molecule as a minute computer. If the number of nuclei in a molecule were, say, ten, each molecule could function as a ten-qubit computer. In Gershenfeld and Chuang's scheme, some $10^{23}$ molecules, working in tandem, all perform the same calculation. The only proviso is that the spin of each nucleus in a computing molecule be in the same state as the spin of its counterpart nucleus in another computing molecule. Other molecules in the sample, whose nuclear spins do not meet that condition, simply do not participate in the computation, and their randomized nuclear spins cancel each other. The pulses that manipulate qubits in the sample each cause a few qubits to decohere, and so with each cycle of computation a few of the redundant molecular computers drop out. But because so many molecules are all performing the same calculation, enough coherent molecules are left to finish the computation, and the signal of the result is strong enough to be measured.

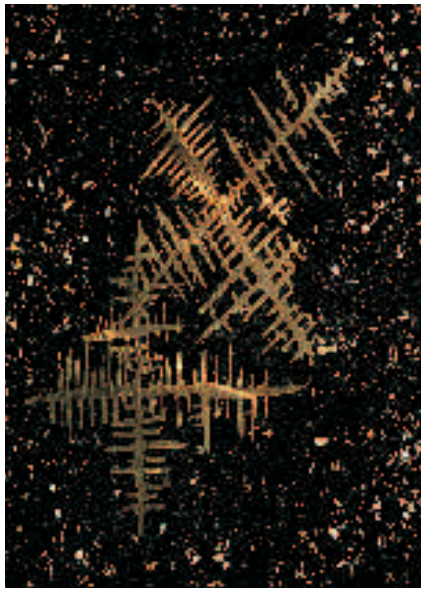
Gershenfeld and Chuang have used quantum algorithms on three qubits; existing NMR spectrometers could readily handle about ten of them. Beyond that the signal strength rapidly decreases. Even a thirty-qubit quantum computer, however, would surpass the speed of ordinary computers for certain problems. "The really hard part of actually building and isolating the system has been done for us by nature," Gershenfeld says—so he and Chuang can concentrate on computation. Although their experiments were done with huge, million-dollar NMR machines, they say a tabletop version of the machine should work just as well. In the future, Gershenfeld speculates, computers will come with a quantum coprocessor that automatically takes over for certain difficult calculations.

—MEHER ANTIA AND PETER G. BROWN

# Galactic Garbo's

*Hubble noses in on reclusive stars*

ALONE. YOUR WORLD IS ALONE. AT night the sky is black, a dome of ebony with no stars. You look up, and only after a long while can you make out the faintest smudges scattered across the heavens. You pull out your binoculars to make sure those distant galaxies are real. After a few long moments of darkness a shooting star streaks by, and its fleeting light seems bright in the empty sky. Later in the night a single object rises, a magnificent diffuse spiral of light, about the size of a nickel held at arm's length. You



*Michele Oka Doner,*
Celestial Plaza (detail), *1995*

take aim at the spiral with your binoculars and finally see other stars, but they are only dots, barely visible in a nearby galaxy.

Such would be the night sky from the solar system of a lone star wandering in the vast space between the galaxies. The existence of such stars was long suspected but, until recently, unproven. Now astronomers observing with the Hubble Space Telescope have identified the first such intergalactic stars, drifting in space in the Virgo Cluster of galaxies, more than 60 million light-years from the earth and more than 300,000 light-years from any large galaxy.

The newly discovered stars showed their faces when astronomers aimed the Hubble telescope at a small but seemingly blank portion of sky near the center of the Virgo cluster. In the ensuing photograph the astronomers saw about 600 dots of extremely faint magnitude, some as dim as 27.8. That was substantially more than the number of comparable dots present in what is called the Hubble Deep Field, a long photographic exposure of a different region of empty sky made by the space telescope over a ten-day period. The astronomers inferred from the difference that the extra dots in Virgo were stars.

The lone rangers are probably not much younger than three billion years, and they have spent most of their lives in intergalactic space. (The Virgo cluster formed between 5 billion and 15 billion years ago.) They are so diffusely scattered that, on average, 1,000 light-years of space separates one star from another. Astronomers suspect that the lone stars are red giants. Because they are probably nearing the end of their lives, they are large and bright, similar to the giant star Betelgeuse in our own galaxy [see Quanta, "Telescopic Vision," by Robert Zimmerman, *The Sciences,* March/April 1996]—and hence visible here on earth.

ASTRONOMERS DOUBT THAT STARS can form in the emptiness between galaxies. Instead, notes the astronomer Harry Ferguson of the Space Telescope Science Institute in Baltimore, Maryland, many of the stars wandered from their birthplace galaxies into intergalactic space "literally because of gravitational confusion." When their home galaxy moved into the center of the Virgo cluster, the stars could no longer distinguish between the gravitational field of their galaxy and that of the cluster's. "When their galaxy moved on," Ferguson concludes, "the star would drift away in a different direction." Other lone stars were flung into intergalactic space when galaxies in the relatively crowded environment of the Virgo cluster either merged or ground past each other. Now, isolated far from any other object, the drift of the lone stars is governed more by the general gravitational field of the Virgo cluster than by that of any particular galaxy.

The astronomers estimate that as many as 10 million more stars could hide in the field covered by the photograph, too dim for Hubble to see. On that basis, they suspect that the entire Virgo cluster, with its 2,500 galaxies, includes some one trillion intergalactic stars, about 10 percent of the cluster's total mass. Unfortunately, though such a huge quantity of matter might seem to add substantially to the total mass of the universe, it is not the so-called missing matter needed to halt the expansion of the big bang and "close" the universe gravitationally. As Ferguson says: "It's only a drop in the bucket."

—ROBERT ZIMMERMAN

# Peer Review

*Continued from Page 5*

¶Hans von Baeyer discusses a recent experiment in which a light beam passes through a double-slit device using a polarizer for each slit and then traverses a third polarizer before reaching a screen. He contends that the results of the experiment imply that light is X percent particle and 100 – X percent wave. Had this ingenious experiment been done even a hundred years ago, however, the results would have caused little surprise; instead, they would have been interpreted as confirming the wave nature of light. Both then and now, the 100 percent wave nature of the electromagnetic field in the experimental setting predicts exactly the effects described in the article.

Complications arise only when, under different experimental circumstances, light acts as a collection of photons rather than as waves. Depending on the nature of such an experiment, beams of light (or of electrons, neutrons and so forth) appear to act either like waves or like particles.

To draw the conclusion, from an experiment in which light acts entirely as a wave, that wave–particle duality occurs because objects are X percent wave and 100 – X percent particle is rather unconvincing.

GEORGE SCHMIDT
*Stevens Institute of Technology*
*Hoboken, New Jersey*

THEODOR TAMIR
*Polytechnic University*
*Brooklyn, New York*

¶I am pleased to have Hans Christian von Baeyer's column back again. I missed it.

ALEX BLUM
*Bar-Ilan University*
*Ramat-Gan, Israel*

**Hans Christian von Baeyer replies:** Mr. Malin is right to point out that in the double-slit experiment quantons "become" particles when they are detected on the screen. The question is: What were they when they passed the slits? With the tagging devices in place and the eraser disabled, one could, in principle, determine which slit a quanton traversed. My implicit assumption is that "which path" information, even in principle, is the hallmark of particles, not of waves.

Messrs. Schmidt and Tamir's remark about the experiment's being done a century ago is prescient in reverse: it *was* performed and analyzed in the way they mentioned by the French physicists François Arago and Augustin Jean Fresnel in 1816, as summarized on page 346 of R. W. Wood's treatise, *Physical Optics*. I adduced it not as a quantum experiment but as an "analogue" in the same sense that Young's classic experiment is the analogue of a double-slit experiment with electrons. As I wrote in my essay: "To change the tabletop analogue into a real quantum-eraser experiment, you would have to take the laws of optics out of the picture by shooting quantons through the slits one at a time."

And thank you, Mr. Blum. I'm happy to be back.

## OENOPREHISTORY

Patrick E. McGovern's story of recent discoveries concerning the early history of wine ["Vin Extraordinaire," November/December 1996] has an importance beyond its undoubted anecdotal and entertainment value. Conventional accounts of what happened in prehistory tend to apply a calorie-driven model, in which farming and urban civilization came about because of the domestication of cereal crops and their intensive cultivation by techniques such as irrigation. The achievement of an agricultural surplus is thus seen as the crucial step. The beginnings of farming in the New World do not correspond well to that pattern, because crops yielding fibers, oils, spices or medicines seem to antedate the large-scale use of maize. Such findings are often seen as local peculiarities. Now, however, it seems that the New World pattern may be more general than the rather puritan vision of "porridge first."

The significant aspect of Mr. McGovern's discovery of wine at Hajji Firuz is that his evidence dates to 5000 B.C., a date contemporaneous with what may be the earliest evidence for irrigation (at Choga Mami, near Mandali in eastern Iraq) and also with the postulated application of intensive cultivation techniques, such as the use of the light plow on the steppes of northern Iraq. This story begins to make geographic sense: an inner zone of intensive cultivation developed around the Fertile Crescent of Greater Mesopotamia, surrounded by an outer zone of more mountainous territory where "variety crops" were being explored.

Information from archaeological organic chemistry is thus vital for understanding the processes that led to dietary variety and to the increasing complexity of the exchanges fueling the emergence of the first urban civilizations in Mesopotamia. Those changes involved an increase in the scale of trading, including the development of bulk transport by river, which led to the world's first use of boats with sails; and the establishment of overland routes, which led to the domestication of the donkey, the camel and perhaps the horse (to provide traders with mules). Although some of the most valuable traded commodities were precious materials such as metals and ornamental stones, the growing quantities of organic products such as dates, figs, olives and grapes—and the products of high value that could be made from them—were as important in Mesopotamia as the trade in tobacco, sugar and tea were in the world economy of the early modern period. Moreover, the intoxicating properties of wine certainly had religious significance, just as other substances with psychotropic effects played a major role in early shamanism.

The realization that residues in early pottery may contain complex and recognizable organic substances thus coincides with a growing interest in the cultural and economic significance of such substances. It is a vital new area of understanding in the development of human societies.

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¶In announcing some remarkable new discoveries about the early history of winemaking, Patrick McGovern justly celebrates the increasing role played by technology in archaeological investigation.

The Godin Tepe wine jar is now well known to specialists, and most of them were probably not very surprised by the discovery. Godin Tepe, in west central Iran, lies outside the posited range of wild grapes, and so the wine was either imported or made from domesticated grapes. The latter possibility is the more likely, because the occurrence of domesticated grapes in western Iran around 3000 B.C. harmonizes with the evidence assembled by archaeobotanists and with early written records from Mesopotamia and Egypt.

The new evidence reported from Hajji Firuz, however, is truly remarkable. First, it pushes the earliest winemaking back some 2,000 years, to the late sixth millennium B.C. Second, the discovery of terebinth resin in the wine residues evinces a sophisticated knowledge of materials and demonstrates that these early winemakers had already solved the problem of wine preservation. Third, the Hajji Firuz wine jars are dated to around 1,000 years earlier than the earliest good evidence for grape domestication.

Were the Hajji Firuz grapes wild or domesticated? Wine made from domesticated grapes in 5000 B.C. would strengthen the hypothesis that grapes were domesticated in multiple regions independently. People in the Near East had probably already been gathering wild grapes for thousands of years. Quite a few American varieties were also domesticated from the wild. (Incidentally, Mr. McGovern's tale of Thomas Jefferson's alleged disillusionment with native American grapes belongs to myth. In fact, Jefferson was a firm believer in the value of native grapes for wine, as a perusal of *Thomas Jefferson's Garden Book* makes clear.)

Nevertheless, it seems doubtful that the Hajji Firuz wine was made from domesticated grapes, because of the virtual absence of supporting archaeobotanical evidence for domestication in the fifth millennium. Claims made in the botanical literature for a much earlier domestication in the Caucasus region have never been substantiated. After all, the ill-fated Samuel Gottlieb

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Gmelin, an eighteenth-century professor of natural history in Saint Petersburg, explored the region south of the Caspian Sea in 1771 and noted that the wines of the Persian province of Gilan were made from the wild grape. If people were still using wild grapes in the late eighteenth century, why not some 7,000 years earlier?

MARVIN A. POWELL
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**Patrick McGovern replies:** More archaeobotanical and archaeochemical sleuthing will be needed to resolve some of the important issues raised by Messrs. Sherratt and Powell. Both disciplines, for instance, must be applied in a much more rigorous and innovative manner before archaeologists will know where the grape was first cultivated or what was the subsequent course of its domestication and transplantation to temperate climates throughout the world. Evidently, all the preconditions for the cultivation of the vine, spurred on by the production and preservation of wine, came together during the Neolithic period in the Near East.

Whether selective plantings of the highly prolific and tasty hermaphroditic domesticated species *Vitis vinifera vinifera* first took place in the Caucasus, or in some other highland area where "variety crops" were being developed, can only be determined by a detailed investigation of the materials available from current and past excavations. Unfortunately, botanical and chemical evidence has often not been collected systematically, and it has sometimes been inadvertently contaminated or destroyed.

In the contemporary post-cold war era it should be possible to reexamine the abundant botanical remains of the grape in the museums and collections of Georgia, Armenia, Azerbaijan and Dagestan, remains that date from the sixth and fifth millennia B.C.

As I and my coauthors argue in an article in the spring 1997 issue of *Expedition* (published by the University of Pennsylvania Museum) and as Mr. Sherratt stresses for the Neolithic, trade probably motivated the transplantation of the domesticated grapevine from its "homeland," wherever that may be, to other areas of the world. As we show in our article, the rulers and upper class first created a market for imported wine; soon thereafter the vine was transplanted and local winemaking developed. That scenario of trade and transplantation, based on the presently available archaeobotanical evidence and the chemical confirmation of wine inside specific pottery vessels used in transporting the wine, suggests that the grape was first domesticated somewhere in northern Mesopotamia or the Caucasus and that cultivation then spread out from there along both arms of the Fertile Crescent in the period from roughly 5000 to 2500 B.C.

Possibly, the Eurasian species was taken into cultivation elsewhere in the modern geographic range of the wild subspecies, even as far west as Spain. It can be proposed that the luscious cabernet sauvignon of southwestern France is a descendant of a separate cultivar that was brought across the Pyrenees. Until more archaeological and scientific research is carried out, this and other possibilities must remain a foretaste of things to come.

It is true, as Mr. Powell points out, that Thomas Jefferson was a great believer in the potential of the "foxy" native American vine, *Vitis labrusca,* and quite possibly introduced hybrids of this and *V. vinifera vinifera,* which still produce fine wines in the Monticello, Virginia, area. *V. labrusca* by itself did not yield a commercially successful wine, but, developed into the Concord grape, it came to undergird the American grape-jelly industry.

New World peoples, long before Thomas Jefferson, had apparently already selected a range of fermented beverages and hallucinogens, which made no use of the many wild grape species growing here. The scientific techniques that have enabled the identification of wine in the Old World are generalizable to the New, where it is quite possible that organics of a less mundane nature than maize were the "engines of culture." •

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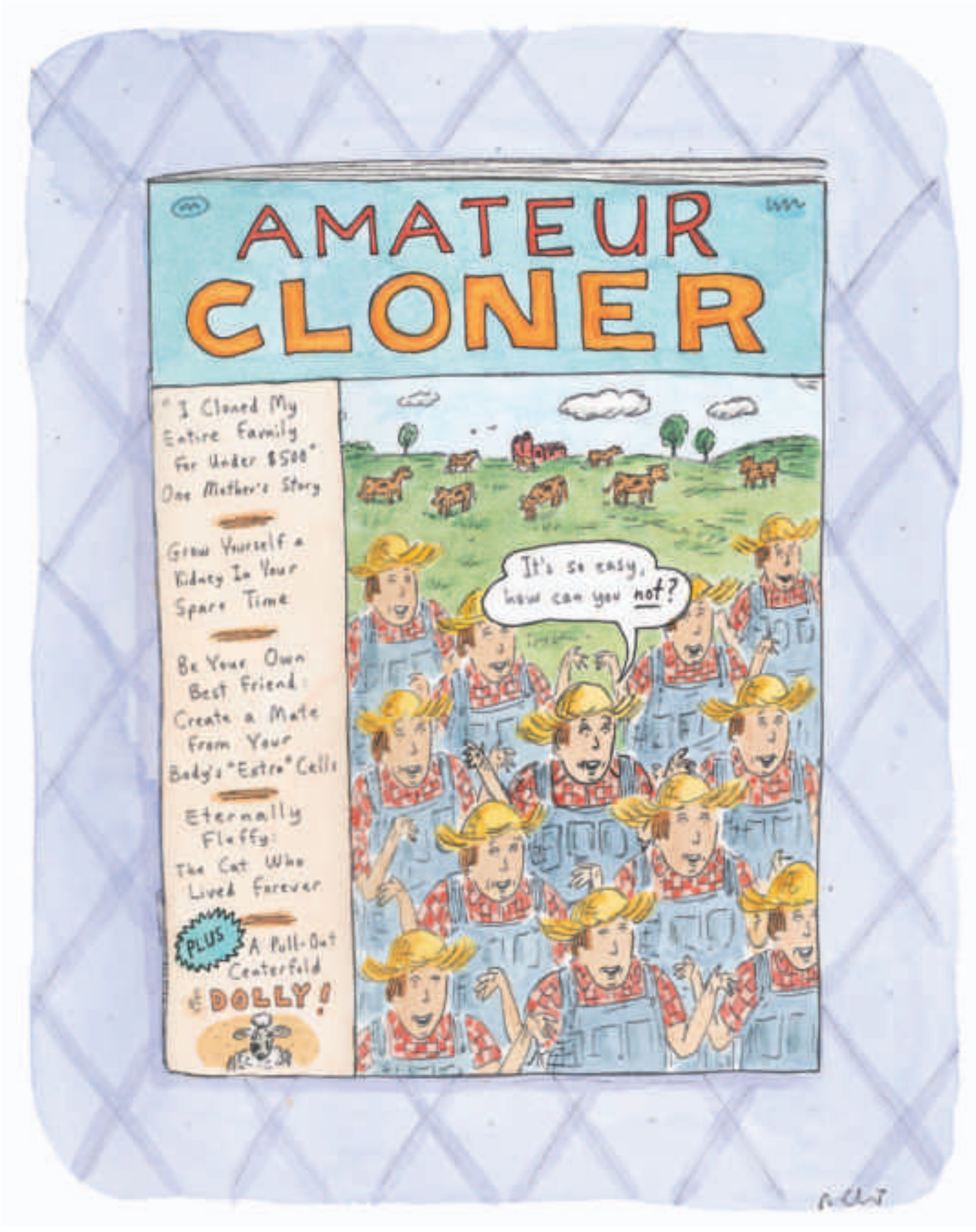
# Strange Matter

ROZ CHAST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